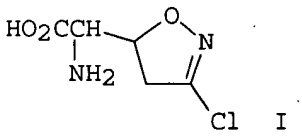
***NOTE to Phyllis: Apparently "Acivacin" was misspelled in the claims. It's not in
Registry, and CAPlus contains only one record for a compound that may be the same, and it's spelled "Acivicin".***

=> d hit acivacin all

L22 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1983:27436 HCAPLUS
DN 98:27436
ED Entered STN: 12 May 1984
TI Biochemical pharmacology of acivicin in rat hepatoma cells
AU Lui, May S.; Kizaki, Harutoshi; Weber, George
CS Sch. Med., Indiana Univ., Indianapolis, IN, 46223, USA
SO Biochemical Pharmacology (1982), 31(21), 3469-73
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
CC 1-6 (Pharmacology)
GI



I

AB The antiglutamine agent acivicin (I) [42228-92-2] inhibited the growth of hepatoma 3924A cells in culture. The 7 day LC50 of acivicin was determined to be 1.4 μM. A combination of cytidine, deoxycytidine, and guanosine completely protected the hepatoma cells against the cytotoxicity acivicin, but each nucleoside by itself had no effect. Acivicin (0.1 mM) inhibited the incorporation of uridine and thymidine into macromols., but not that of leucine. Acivicin depressed the pools of CTP, GTP, dCTP, dGTP, and dTTP, but it increased the UTP levels. The activity of a highly purified CTP synthetase (EC 6.3.4.2) [9023-56-7] from rat liver and hepatoma 3924A was inhibited by acivicin. The inhibition was competitive with respect to L-glutamine, and the Ki values were 1.1 and 3.6 μM, resp. hydroxyacivicin [54549-02-9] Was also a competitive inhibitor, but it was less effective than acivicin, with a Ki value of 1.8 mM for the hepatoma enzyme. It appears that the principal mechanism of action of **acivacin** is the inhibition of CTP synthetase and GMP synthetase (EC 6.3.5.2) [37318-71-1].
ST acivicin antitumor biochem pharmacol
IT Neoplasm inhibitors
(hepatoma, acivicin, biochem. mechanism of)
IT 54549-02-9
RL: BIOL (Biological study)
(CTP synthetase inhibition by, hepatoma inhibition in relation to)
IT 42228-92-2
RL: BIOL (Biological study)
(hepatoma inhibition by, biochem. mechanism of)
IT 9023-56-7 37318-71-1
RL: BIOL (Biological study)

(inhibition of, by acivicin, hepatoma inhibition in relation to)

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L1             1 SEA FILE=REGISTRY ABB=ON  ETHACRYNIC ACID/CN
L2             1 SEA FILE=REGISTRY ABB=ON  PDTC/CN
L4             1 SEA FILE=REGISTRY ABB=ON  2,3-DIMERCAPTO-1-PROPANESULFONIC
                 ACID/CN
L5             1 SEA FILE=REGISTRY ABB=ON  DITHIOCARBAMATE/CN
L6             1 SEA FILE=REGISTRY ABB=ON  DITHIOTHREITOL/CN
L8             1 SEA FILE=REGISTRY ABB=ON  BUTHIONINE SULFOXIMINE/CN
L9             1 SEA FILE=REGISTRY ABB=ON  METHIONINE SULFOXIMINE/CN
L11            1 SEA FILE=REGISTRY ABB=ON  N-ACETYLCYSTEINE/CN
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L13            2 SEA FILE=REGISTRY ABB=ON  LIPOIC ACID/CN
L14            1 SEA FILE=REGISTRY ABB=ON  THIOCTIC ACID/CN
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                 L21 OR L23
L25        23859 SEA FILE=HCAPLUS ABB=ON  L24
L26       146867 SEA FILE=HCAPLUS ABB=ON  L25 OR (?ETHACRYNIC? OR (2,3-DIMERCAPT
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                 OR ?DITHIOCARBAMATE? OR ?DITHIOTHREITOL? OR ?GLUTATHIONE? OR
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                 EINE? OR NAC OR ?CYSTEAMINE?)
L27       149253 SEA FILE=HCAPLUS ABB=ON  L26 OR (?LIPOIC? OR ?THIOCTIC? OR
                 2-MERCAPTO-1-PROPANESULFONIC?)(W)?ACID? OR DMSA OR MESNA OR
                 ?REDUC?(W)?CYSTEINE? OR ?ACIVACIN? OR ?ACIVICIN?
L28         7586 SEA FILE=HCAPLUS ABB=ON  L27 AND ?REDOX?
L29         1110 SEA FILE=HCAPLUS ABB=ON  L28 AND (?CANCER? OR ?CARCIN? OR
                 ?NEOPLAS? OR ?TUMOR? OR ?TUMOUR?)
L30          199 SEA FILE=HCAPLUS ABB=ON  L29 AND ?PROLIFERAT?
L31           48 SEA FILE=HCAPLUS ABB=ON  L30 AND ?THIOL?
L34           54 SEA FILE=HCAPLUS ABB=ON  L30 AND (PRD<19990216 OR PD<19990216)
L35           85 SEA FILE=HCAPLUS ABB=ON  L31 OR L34
L36           54 SEA FILE=HCAPLUS ABB=ON  L35 AND (PRD<19990216 OR PD<19990216)

=> d ibib abs l36 1-54

L36  ANSWER 1 OF 54  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:248644  HCAPLUS
DOCUMENT NUMBER:          142:274057
TITLE:                    Sequences of human schizophrenia related genes and use
                          for diagnosis, prognosis and therapy
INVENTOR(S):              Liew, Choong-chin
PATENT ASSIGNEE(S):       Chondrogene Limited, Can.
SOURCE:                   U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S.
                          Ser. No. 802,875.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   46
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
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| US 2004241727 | A1 | 20041202 | US 2004-812731 | | 20040330 <-- |
| US 2004014059 | A1 | 20040122 | US 2002-268730 | | 20021009 <-- |
| US 2005191637 | A1 | 20050901 | US 2004-803737 | | 20040318 <-- |
| US 2005196762 | A1 | 20050908 | US 2004-803759 | | 20040318 <-- |
| US 2005196763 | A1 | 20050908 | US 2004-803857 | | 20040318 <-- |
| US 2005196764 | A1 | 20050908 | US 2004-803858 | | 20040318 <-- |
| US 2004241727 | A1 | 20041202 | US 2004-812731 | | 20040330 <-- |
| PRIORITY APPLN. INFO.: | | | US 1999-115125P | P | 19990106 <-- |
| | | | US 2000-477148 | B1 | 20000104 |
| | | | US 2002-268730 | A2 | 20021009 |
| | | | US 2003-601518 | A2 | 20030620 |
| | | | US 2004-802875 | A2 | 20040312 |
| | | | US 2004-812731 | A | 20040330 |

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of 3 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L36 ANSWER 2 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:248643 HCAPLUS
DOCUMENT NUMBER: 142:274056
TITLE: Sequences of human schizophrenia related genes and use for diagnosis, prognosis and therapy
INVENTOR(S): Liew, Choong-Chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
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| US 2004241727 | A1 | 20041202 | US 2004-812731 | | 20040330 <-- |
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| US 2005196763 | A1 | 20050908 | US 2004-803857 | | 20040318 <-- |
| US 2005196764 | A1 | 20050908 | US 2004-803858 | | 20040318 <-- |
| US 2004241727 | A1 | 20041202 | US 2004-812731 | | 20040330 <-- |
| PRIORITY APPLN. INFO.: | | | US 1999-115125P | P | 19990106 <-- |
| | | | US 2000-477148 | B1 | 20000104 |
| | | | US 2002-268730 | A2 | 20021009 |
| | | | US 2003-601518 | A2 | 20030620 |
| | | | US 2004-802875 | A2 | 20040312 |
| | | | US 2004-812731 | A | 20040330 |

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific

primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of 3 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L36 ANSWER 3 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:172213 HCAPLUS
DOCUMENT NUMBER: 142:259426
TITLE: Gene expression profiles and biomarkers for the detection of asthma-related and other disease-related gene transcripts in blood
INVENTOR(S): Liew, Choong-Chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| US 2005042630 | A1 | 20050224 | US 2004-816357 | 20040401 <-- |
| US 2004014059 | A1 | 20040122 | US 2002-268730 | 20021009 <-- |
| US 2005191637 | A1 | 20050901 | US 2004-803737 | 20040318 <-- |
| US 2005196762 | A1 | 20050908 | US 2004-803759 | 20040318 <-- |
| US 2005196763 | A1 | 20050908 | US 2004-803857 | 20040318 <-- |
| US 2005196764 | A1 | 20050908 | US 2004-803858 | 20040318 <-- |
| US 2005042630 | A1 | 20050224 | US 2004-816357 | 20040401 <-- |
| PRIORITY APPLN. INFO.: | | | US 1999-115125P | P 19990106 <-- |
| | | | US 2000-477148 | B1 20000104 |
| | | | US 2002-268730 | A2 20021009 |
| | | | US 2003-601518 | A2 20030620 |
| | | | US 2004-802875 | A2 20040312 |
| | | | US 2004-816357 | A 20040401 |

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing, and monitoring diseases, and in particular asthma, using gene-specific and/or tissue-specific primers. Affymetrix Human Genome U133 and ChondroChip microarrays were used to detect differentially expressed gene transcripts in hypertension, obesity, allergy, systemic steroids, coronary artery disease, diabetes type 2, hyperlipidemia, lung disease, bladder **cancer**, rheumatoid arthritis, osteoarthritis, liver **cancer**, schizophrenia, Chagas disease, asthma, and manic depression syndrome. The present invention describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the docoment and publication system constraints.].

L36 ANSWER 4 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:160724 HCAPLUS

DOCUMENT NUMBER: 142:259424
TITLE: Gene expression profiles and biomarkers for the detection of asthma-related and other disease-related gene transcripts in blood
INVENTOR(S): Liew, Choong-Chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE | |
|---|---|---|---|---|---|---|
| US 2005042630 | A1 | 20050224 | US 2004-816357 | | 20040401 | <-- |
| US 2004014059 | A1 | 20040122 | US 2002-268730 | | 20021009 | <-- |
| US 2005191637 | A1 | 20050901 | US 2004-803737 | | 20040318 | <-- |
| US 2005196762 | A1 | 20050908 | US 2004-803759 | | 20040318 | <-- |
| US 2005196763 | A1 | 20050908 | US 2004-803857 | | 20040318 | <-- |
| US 2005196764 | A1 | 20050908 | US 2004-803858 | | 20040318 | <-- |
| US 2004265869 | A1 | 20041230 | US 2004-812716 | | 20040330 | <-- |
| US 2005042630 | A1 | 20050224 | US 2004-816357 | | 20040401 | <-- |
| US 2005042630 | A1 | 20050224 | US 2004-816357 | | 20040401 | <-- |
| PRIORITY APPLN. INFO.: | | | US 1999-115125P | P | 19990106 | <-- |
| | | | US 2000-477148 | B1 | 20000104 | |
| | | | US 2002-268730 | A2 | 20021009 | |
| | | | US 2003-601518 | A2 | 20030620 | |
| | | | US 2004-802875 | A2 | 20040312 | |
| | | | US 2004-816357 | A | 20040401 | |

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing, and monitoring diseases, and in particular asthma, using gene-specific and/or tissue-specific primers. Affymetrix Human Genome U133 and ChondroChip microarrays were used to detect differentially expressed gene transcripts in hypertension, obesity, allergy, systemic steroids, coronary artery disease, diabetes type 2, hyperlipidemia, lung disease, bladder **cancer**, rheumatoid arthritis, osteoarthritis, liver **cancer**, schizophrenia, Chagas disease, asthma, and manic depression syndrome. The present invention describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the docoment and publication system constraints.].

L36 ANSWER 5 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:156228 HCAPLUS
Correction of: 2005:16967
DOCUMENT NUMBER: 142:192331
Correction of: 142:108390
TITLE: Quantitative RT-PCR method for the detection in blood of microarray-identified rheumatoid arthritis-related gene transcripts for diagnosing and monitoring disease state
INVENTOR(S): Liew, Choong-Chin

PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 81 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE | |
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| | | | US 2000-477148 | B1 | 20000104 | |
| | | | US 2002-268730 | A2 | 20021009 | |
| | | | US 2003-601518 | A2 | 20030620 | |
| | | | US 2004-802875 | A2 | 20040312 | |
| | | | US 2004-812782 | A | 20040330 | |

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood for diagnosing and monitoring diseases. The present invention demonstrates that a simple drop of blood may be used to determine the quant. expression of various mRNAs that reflect the health/disease state of the subject through the use of quant. reverse transcription-polymerase chain reaction (QRT-PCR) anal. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring rheumatoid arthritis using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen.

L36 ANSWER 6 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:155679 HCAPLUS
DOCUMENT NUMBER: 142:213366
TITLE: Quantitative RT-PCR method for the detection in blood of microarray-identified rheumatoid arthritis-related gene transcripts for diagnosing and monitoring disease state
INVENTOR(S): Liew, Choong-Chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 81 pp., Cont.-in-part of U.S. Ser. No. 802,875
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| US 2005003394 | A1 | 20050106 | US 2004-812782 | | 20040330 <-- |
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| US 2005003394 | A1 | 20050106 | US 2004-812782 | | 20040330 <-- |
| PRIORITY APPLN. INFO.: | | | US 1999-115125P | P | 19990106 <-- |
| | | | US 2000-477148 | B1 | 20000104 |
| | | | US 2002-268730 | A2 | 20021009 |
| | | | US 2003-601518 | A2 | 20030620 |
| | | | US 2004-802875 | A2 | 20040312 |
| | | | US 2004-812782 | A | 20040330 |

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood for diagnosing and monitoring diseases. The present invention demonstrates that a simple drop of blood may be used to determine the quant. expression of various mRNAs that reflect the health/disease state of the subject through the use of quant. reverse transcription-polymerase chain reaction (QRT-PCR) anal. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring rheumatoid arthritis using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of 3 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L36 ANSWER 7 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:112850 HCAPLUS
DOCUMENT NUMBER: 142:153469
TITLE: Gene expression profiles and biomarkers for the detection of lung disease-related and other disease-related gene transcripts in blood
INVENTOR(S): Liew, Choong-chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 155 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
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| PRIORITY APPLN. INFO.: | | | US 1999-115125P | P | 19990106 <-- |
| | | | US 2000-477148 | B1 | 20000104 |
| | | | US 2002-268730 | A2 | 20021009 |
| | | | US 2003-601518 | A2 | 20030620 |
| | | | US 2004-802875 | A2 | 20040312 |

US 2004-812764 A 20040330

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. Affymetrix Human Genome U133 and ChondroChip microarrays were used to detect differentially expressed gene transcripts in hypertension, obesity, allergy, systemic steroids, coronary artery disease, diabetes type 2, hyperlipidemia, lung disease, bladder **cancer**, rheumatoid arthritis, osteoarthritis, liver **cancer**, schizophrenia, Chagas disease, asthma, and manic depression syndrome. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of 3 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L36 ANSWER 8 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:60759 HCAPLUS
Correction of: 2004:1036572
DOCUMENT NUMBER: 142:111840
Correction of: 142:16824
TITLE: Gene expression profiles and biomarkers for the detection of lung disease-related and other disease-related gene transcripts in blood
INVENTOR(S): Liew, Choong-Chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can
SOURCE: U.S. Pat. Appl. Publ., 155 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE | |
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| | | | US 2000-477148 | B1 | 20000104 | |
| | | | US 2002-268730 | A2 | 20021009 | |
| | | | US 2003-601518 | A2 | 20030620 | |
| | | | US 2004-802875 | A2 | 20040312 | |
| | | | US 2004-812764 | A | 20040330 | |

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. Affymetrix Human Genome U133 and ChondroChip microarrays were

used to detect differentially expressed gene transcripts in hypertension, obesity, allergy, systemic steroids, coronary artery disease, diabetes type 2, hyperlipidemia, lung disease, bladder **cancer**, rheumatoid arthritis, osteoarthritis, liver **cancer**, schizophrenia, Chagas disease, asthma, and manic depression syndrome. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen.

L36 ANSWER 9 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:60754 HCAPLUS
Correction of: 2004:1036571
DOCUMENT NUMBER: 142:233342
Correction of: 142:16836
TITLE: Sequences of human schizophrenia related genes and use for diagnosis, prognosis and therapy
INVENTOR(S): Liew, Choong-Chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE | |
|---|---|---|---|---|---|---|
| US 2004241727 | A1 | 20041202 | US 2004-812731 | | 20040330 | <-- |
| US 2004014059 | A1 | 20040122 | US 2002-268730 | | 20021009 | <-- |
| US 2005191637 | A1 | 20050901 | US 2004-803737 | | 20040318 | <-- |
| US 2005196762 | A1 | 20050908 | US 2004-803759 | | 20040318 | <-- |
| US 2005196763 | A1 | 20050908 | US 2004-803857 | | 20040318 | <-- |
| US 2005196764 | A1 | 20050908 | US 2004-803858 | | 20040318 | <-- |
| US 2004241727 | A1 | 20041202 | US 2004-812731 | | 20040330 | <-- |
| US 2004241727 | A1 | 20041202 | US 2004-812731 | | 20040330 | <-- |
| US 2004265869 | A1 | 20041230 | US 2004-812716 | | 20040330 | <-- |
| PRIORITY APPLN. INFO.: | | | US 1999-115125P | P | 19990106 | <-- |
| | | | US 2000-477148 | B1 | 20000104 | |
| | | | US 2002-268730 | A2 | 20021009 | |
| | | | US 2003-601518 | A2 | 20030620 | |
| | | | US 2004-802875 | A2 | 20040312 | |
| | | | US 2004-812731 | A | 20040330 | |

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of 3 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L36 ANSWER 10 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:796242 HCAPLUS
DOCUMENT NUMBER: 139:302975

TITLE: Regulated expression systems for identification, screening, and directed synthesis of stabilized bioactive peptides for therapeutic use
INVENTOR(S): Altman, Elliot
PATENT ASSIGNEE(S): The University of Georgia Research Foundation, Inc, USA
SOURCE: U.S. Pat. Appl. Publ., 68 pp., Cont.-in-part of U.S. Ser. No. 701,947.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003190740 | A1 | 20031009 | US 2002-210023 | 20020731 <-- |
| WO 2000022112 | A1 | 20000420 | WO 1999-US23731 | 19991012 <-- |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1566438 | A2 | 20050824 | EP 2005-11384 | 19991012 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| US 6818611 | B1 | 20041116 | US 2000-701947 | 20001205 <-- |
| CA 2493306 | AA | 20040205 | CA 2003-2493306 | 20030730 |
| WO 2004011485 | A2 | 20040205 | WO 2003-US23875 | 20030730 |
| WO 2004011485 | A3 | 20050414 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1537137 | A2 | 20050608 | EP 2003-772125 | 20030730 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |

| PRIORITY APPLN. INFO.: | | |
|---|---|---|
| US 1998-104013P | P | 19981013 <-- |
| US 1998-112150P | P | 19981214 <-- |
| WO 1999-US23731 | W | 19991012 |
| US 2000-701947 | A2 | 20001205 |
| EP 1999-951940 | A3 | 19991012 |
| US 2002-210023 | A | 20020731 |
| WO 2003-US23875 | W | 20030730 |

AB An intracellular selection system allows screening for peptide bioactivity and stability. Randomized recombinant peptides are screened for bioactivity in a tightly regulated expression system, preferably derived from the wild-type lac operon. Bioactive peptides thus identified are inherently protease- and peptidase-resistant. Also provided are bioactive

peptides stabilized by a stabilizing group at the N-terminus, the C-terminus, or both. The stabilizing group can be a small stable protein, such as the Rop protein, **glutathione** sulfotransferase, **thioredoxin**, maltose binding protein, or **glutathione** reductase, an α-helical moiety, or one or more proline residues. Construction and characterization of a highly regulatable expression vector, pLAC11, and its multipurpose derivs., pLAC22 and pLAC33, is described. An in vivo approach for generating novel bioactive peptides that inhibit the growth of E. coli is disclosed. Directed synthesis of stable synthetically engineered inhibitor peptides is described.

L36 ANSWER 11 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:373944 HCAPLUS
DOCUMENT NUMBER: 133:118600
TITLE: Liver immunity and **glutathione**
AUTHOR(S): Yamauchi, Akira; Tsuyuki, Shigeru; Inamoto, Takashi; Yamaoka, Yoshio
CORPORATE SOURCE: Department of Gastroenterological Surgery, Graduate School of Medicine, Kyoto University, Kyoto, 606-8507, Japan
SOURCE: Antioxidants & Redox Signaling (**1999**), 1(2), 245-253
CODEN: ARSIF2; ISSN: 1523-0864
PUBLISHER: Mary Ann Liebert
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 49 refs. **Redox** processes have been implicated in various biol. processes, including signal transduction, gene expression, and cell **proliferation**, and several mols. have been identified as **redox** regulators in cell activation. **Glutathione** is the oldest and most investigated mol. among them. Although details of the mechanisms by which **glutathione** regulates various aspects of cell biol. remains to be characterized, the relationship between immunodeficiency and cellular **glutathione** status is well established. **Redox** dysregulation contributes to the pathogenesis of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus (HIV)-infected patients and simian immunodeficiency virus (SIV)-infected rhesus macaques have, on the average, significantly decreased plasma cysteine and intracellular **glutathione** levels. Liver contains abundant levels of reducing factors. However, **glutathione** levels in serum and peripheral blood mononuclear cells of cirrhosis patients are lower compared to values detected in healthy individuals. In the present article, the significance of **glutathione** in regulating the functions of lymphocytes, especially those of liver-associated lymphocytes, has been described. A novel strategy for immune therapy of liver **neoplasms** with the use of **redox** -modulating agents has been proposed.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 12 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:312371 HCAPLUS
DOCUMENT NUMBER: 133:100789
TITLE: Modulation of DNA repair and **glutathione** levels in human keratinocytes by micromolar arsenite
AUTHOR(S): Snow, Elizabeth T.; Hu, Yu; Yan, Chong Chao; Chouchane, Salem
CORPORATE SOURCE: Nelson Institute of Environmental Medicine, New York University School of Medicine, Tuxedo, NY, 10987, USA

SOURCE: Arsenic Exposure and Health Effects, Proceedings of the International Conference on Arsenic Exposure and Health Effects, 3rd, San Diego, July 12-15, 1998 ( **1999**), Meeting Date 1998, 243-251. Editor(s): Chappell, Willard R.; Abernathy, Charles O.; Calderon, Rebecca L. Elsevier Science Ltd.: Oxford, UK.
CODEN: 68YOAM
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Arsenic (As) is a human **carcinogen**, but not a mutagen, although it inhibits DNA repair and is a comutagen. Human AG06 keratinocytes treated with micromolar arsenic exhibit dose and time-dependent loss of DNA ligase function. However, purified human DNA ligase I, ligase III, and other repair enzymes such as DNA polymerase β, are not inhibited by less than millimolar arsenite, As(III), the most toxic form of As found in the environment. DNA ligase activity in exts. from untreated keratinocytes is also insensitive to less than millimolar As. Pyruvate dehydrogenase, on the other hand, is inhibited by micromolar As and probably dets. As-induced cytotoxicity. Simultaneous treatment of AG06 cells with an alkylating agent, 1-methyl-3-nitro-1-nitrosoguanidine (MNNG), plus As produces a synergistic increase in viability (dye uptake) at low doses and a synergistic increase in toxicity at high doses. Micromolar As also modulates cellular **redox** levels and induces a variety of cellular stress response genes. Keratinocytes treated with As exhibit both a time- and dose-dependent increase in cellular GSH levels and alterations in the relative activity of several GSH-dependent enzymes. These As-induced changes in cellular **redox** capacity and DNA repair activity are not directly related to toxicity. Maximal induction of GSH and DNA repair occurs after treatment with sub-toxic concns. of As. At submicromolar concns., arsenic also induces **hyperproliferation** of keratinocytes, both in vivo and in vitro. These results suggest that As modulates DNA repair and **redox** levels primarily through post-translational or transcriptional mechanisms.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 13 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:141601 HCAPLUS
Correction of: 1996:263007
DOCUMENT NUMBER: 132:150093
Correction of: 124:314095
TITLE: Reduction-oxidation (**redox**) state regulation of extracellular matrix metalloproteinases and tissue inhibitors in cardiac normal and transformed fibroblast cells
AUTHOR(S): Tyagi, Suresh C.; Kumar, G. Suresh; Broders, Susan
CORPORATE SOURCE: Dalton Cardiovascular Research Center, University Missouri-Columbia, Columbia, MO, 65212, USA
SOURCE: Journal of Cellular Biochemistry (**1996**), 61(1), 139-151
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Latent matrix metalloproteinases (MMPs) in normal myocardium are activated in end-stage heart failure. In vitro oxidized **glutathione** (GSSG) activates myocardial MMPs which contains a cysteine residue. In vivo GSSG induce the collagen lysis and cardiac dilatation. To assess whether **thiol** and non-**thiol** reducing agents have

direct effect on the interstitial human heart fibroblast (HHF) **proliferation** and MMP expression, HHF and polyoma virus transformed fibroblast cells were cultured with or without the **thiol**-containing reduced (GSH) or oxidized (GSSG) **glutathiones**, pyrrolidine **dithiocarbamate** (PDTC) and N-acetylcysteilne (**NAC**), and non-**thiol** ascorbic acid. After 100 μg/mL (.apprx.0.3 mM) GSH or PDTC treatment the **proliferative** (synthetic) phenotype of transformed fibroblast cells was changed to quiescent (contractile) phenotype. Also, after GSH, PDTC, and ascorbic acid treatment the medium was then analyzed for MMP activity by zymog. The results indicate reduction in MMP expression in transformed fibroblast cells after GSH and PDTC treatments and no effect after ascorbic acid treatment. Based on reverse zymog., we observed the level of tissue inhibitor of metalloproteinase (TIMP) at a decreased level in transformed cells. The effect of the reducing agent at the gene transcription was measured by estimating mRNA (Northern blot anal.) of MMP and of TIMP in the cells that were cultured in medium in the presence and absence of GSH. These results indicate that GSH induces MMP-2 and MMP-1 expression in normal HHF and that GSH reduces MMP-2 and MMP-1 in transformed fibroblast cells. After the treatment, the TIMP-2 level was repressed in normal HHF and TIMP-2 level increased in transformed fibroblast cells. These events are dependent on the nuclear transcription factor activity on the collagenase promoter in normal HHF cells. On the other hand, in polyoma transform fibroblast cells these events are not dependent on this collagenase promoter. These results suggest that oxidative environment induces normal HHF cell **proliferation**, and the reducing agent decreases normal HHF cell **proliferation** by inducing MMP and repressing TIMP gene transcription. In transformed cells reducing agents inhibit MMP expression and increase TIMP levels, which suggests a role of antioxidants in preventing **tumorigenesis.**

L36 ANSWER 14 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:98240 HCAPLUS
DOCUMENT NUMBER: 132:146655
TITLE: Inhibitors of **redox** signaling for restoration of apoptosis and inhibition of abnormal cell **proliferation**
INVENTOR(S): Kirkpatrick, D. Lynn; Powis, Garth
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000006088 | A2 | 20000210 | WO 1999-US17496 | 19990802 <-- |
| WO 2000006088 | A3 | 20000615 | | |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
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| US 6372772 | B1 | 20020416 | US 1998-127219 | | 19980731 <-- |
| CA 2339233 | AA | 20000210 | CA 1999-2339233 | | 19990802 <-- |
| AU 9954630 | A1 | 20000221 | AU 1999-54630 | | 19990802 <-- |
| PRIORITY APPLN. INFO.: | | | US 1997-54566P | P | 19970801 <-- |
| | | | US 1998-127219 | A | 19980731 <-- |
| | | | WO 1999-US17496 | W | 19990802 |

AB The present invention is directed to a composition or formulation which inhibits or interferes with cellular **redox** function, and method of using same to restore normal cellular function. More specifically, the composition of the present invention interferes with or inhibits abnormal cellular **proliferation** and or restores cellular apoptosis.

L36 ANSWER 15 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:778665 HCAPLUS
DOCUMENT NUMBER: 132:147086
TITLE: Increased **glutathione** synthesis associated with platelet-derived growth factor stimulation of NIH3T3 fibroblasts
AUTHOR(S): Iantomasi, T.; Favilli, F.; Degl'Innocenti, D.; Vincenzini, M. T.
CORPORATE SOURCE: viale Morgagni 50, Department of Biochemical Sciences, University of Florence, Florence, 50134, Italy
SOURCE: Biochimica et Biophysica Acta, Molecular Cell Research (**1999**), 1452(3), 303-312
CODEN: BBAMCO; ISSN: 0167-4889
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous data show a relation between GSH content and **proliferation** of normal and **tumor** cells. We recently demonstrated a specific involvement of GSH in the autophosphorylation activity of the platelet-derived growth factor (PDGF) receptor in NIH3T3 fibroblasts. In this study we demonstrate that the stimulation by PDGF of serum-starved NIH3T3 cells increases cellular GSH content, while no change in oxidized GSH content was measured. Expts. performed with actinomycin, cycloheximide and buthionine sulfoximide, a specific inhibitor of the rate-limiting enzyme of the de novo synthesis of GSH γ-glutamylcysteine synthetase (γ-GCS), confirm PDGF induction of GSH synthesis. These results provide the first demonstration that PDGF mediated transduction signals seem strictly related to mechanisms involved in the increase of γ-GCS activity associated with increased γ-GCS heavy subunit mRNA levels. In fact, serum and epidermal growth factor (EGF) stimulation of quiescent NIH3T3 and NIH3T3, which overexpress EGF receptor, does not affect GSH content or its synthesis. These data may be related to a possible GSH role in the **redox** regulation of cell **proliferation** mediated by PDGF.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 16 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:582008 HCAPLUS
DOCUMENT NUMBER: 131:333310
TITLE: Effect of Thioacetamide on the Hepatic Expression of γ-Glutamylcysteine Synthetase Subunits in the Rat
AUTHOR(S): Lu, Shelly C.; Huang, Zong-Zhi; Yang, Heping; Tsukamoto, Hidekazu
CORPORATE SOURCE: Division of Gastroenterology and Liver Diseases, USC Liver Disease Research Center, USC School of Medicine,

Los Angeles, CA, 90033, USA
SOURCE: Toxicology and Applied Pharmacology (**1999**), 159(3), 161-168
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Glutathione** (GSH) is the main non-protein **thiol** important in antioxidant defense and maintenance of the intracellular **redox** state. A major determinant of the rate of GSH synthesis is the activity of the rate-limiting enzyme, γ-glutamylcysteine synthetase (GCS). A heavy (HS) and light subunit (LS) make up GCS; oxidative stress regulates both transcriptionally. cis-Acting elements important for the oxidative stress-induced transcriptional up-regulation of both subunits are antioxidant response element (ARE) and activator protein-1 (AP-1) site. The nuclear factor-κB (NF-κB) binding site may also regulate the heavy subunit. Increased GSH and γ-glutamyltranspeptidase are often observed in **preneoplastic** hepatocyte nodules and may be important in **hepatocarcinogenesis.** The current work examined the effect of a commonly used **hepatocarcinogen**, thioacetamide (TAA), on the expression of GCS subunits. After 3 wk of TAA treatment, liver GSH level remained unchanged despite significant oxidative stress as measured by the thiobarbituric acid reactive substance assay. The mRNA levels of GCS-HS and GCS-LS increased six- and fourfold, resp., and the protein level of GCS-HS and GCS activity all increased. Electrophorectic mobility shift assay showed binding to ARE, AP-1, and NF-κB probes all increased. These results suggest TAA treatment increased hepatic GCS subunit expression and GCS activity by inducing oxidative stress and increasing the binding to **redox**-sensitive cis-acting elements important for transcriptional up-regulation of GCS. This is the first in vivo study that examined the effect of a **hepatocarcinogen** on GCS expression. (c) 1999 Academic Press.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 17 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:569467 HCAPLUS
DOCUMENT NUMBER: 131:320870
TITLE: **Redox** modulation of cell surface protein **thiols** in U937 lymphoma cells: the role of γ-glutamyl transpeptidase-dependent H2O2 production and S-**thiolation**
AUTHOR(S): Dominici, S.; Valentini, M.; Maellaro, E.; Del Bello, B.; Paolicchi, A.; Lorenzini, E.; Tongiani, R.; Comporti, M.; Pompella, A.
CORPORATE SOURCE: Institute of General Pathology, University of Siena, Siena, Italy
SOURCE: Free Radical Biology & Medicine (**1999**), 27(5/6), 623-635
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The expression of gamma-glutamyl transpeptidase (GGT), a plasma membrane ectoenzyme involved in the metabolism of extracellular reduced **glutathione** (GSH), is a marker of **neoplastic** progression in several exptl. models, and occurs in a number of human malignant **neoplasms** and their metastases. Because it favors the supply of

precursors for the synthesis of GSH, GGT expression has been interpreted as a member in cellular antioxidant defense systems. However, **thiol** metabolites generated at the cell surface during GGT activity can induce prooxidant reactions, leading to production of free radical oxidant species. The present study was designed to characterize the prooxidant reactions occurring during GGT ectoactivity, and their possible effects on the **thiol redox** status of proteins of the cell surface. Results indicate that: (i) in U937 cells, expressing significant amts. of membrane-bound GGT, GGT-mediated metabolism of GSH is coupled with the extracellular production of hydrogen peroxide; (ii) GGT activity also results in decreased levels of protein **thiols** at the cell surface; (iii) GGT-dependent decrease in protein **thiols** is due to sulfhydryl oxidation and protein S-**thiolation** reactions; and (iv) GGT irreversible inhibition by **acivicin** is sufficient to produce an increase of protein **thiols** at the cell surface. Membrane receptors and transcription factors have been shown to possess critical **thiols** involved in the transduction of **proliferative** signals. Furthermore, it was suggested that S-**thiolation** of cellular proteins may represent a mechanism for protection of vulnerable **thiols** against irreversible damage by prooxidant agents. Thus, the findings reported here provide addnl. explanations for the envisaged role played by membrane-bound GGT activity in the **proliferative** attitude of malignant cells and their resistance to prooxidant drugs and radiation therapy.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 18 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:467538 HCAPLUS
DOCUMENT NUMBER: 131:241212
TITLE: Differential reconstitution of mitochondrial respiratory chain activity and plasma **redox** state by cysteine and ornithine in a model of **cancer** cachexia
AUTHOR(S): Ushmorov, Alexej; Hack, Volker; Droge, Wulf
CORPORATE SOURCE: Deutsches Krebsforschungszentrum, Division of Immunochemistry, Heidelberg, D-69120, Germany
SOURCE: Cancer Research (**1999**), 59(14), 3527-3534
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism of wasting, as it occurs in malignant diseases and various etiol. unrelated conditions, is still poorly understood. The authors have, therefore, studied putative cause/effect relationships in a murine model of **cancer** cachexia, C57BL/6 mice bearing the fibrosarcoma MCA-105. The plasma of these mice showed decreased albumin and increased glutamate levels, which are typically found in practically all catabolic conditions. Skeletal muscles from **tumor**-bearing mice were found to have an abnormally low mitochondrial respiratory chain activity (mito.RCA) and significantly decreased **glutathione** (GSH) levels. The decrease in mito.RCA was correlated with an increase in the i.m. GSH disulfide/GSH ratio, the plasma cystine/**thiol** ratio, and the GSH disulfide/GSH ratio in the bile. This is indicative of a generalized shift in the **redox** state extending through different body fluids. Treatment of **tumor**-bearing mice with ornithine, a precursor of the radical scavenger spermine, reversed both the decrease in mito.RCA and the change in the **redox** state, whereas treatment with cysteine, a GSH precursor, normalized only the **redox** state.

Treatment of normal mice with difluoromethyl-ornithine, a specific inhibitor of ornithine decarboxylase and spermine biosynthesis, inhibited the mito.RCA in the skeletal muscle tissue, thus illustrating the importance of the putrescine/spermine pathway in the maintenance of mito.RCA. Ornithine, cysteine, and N-acetyl-cysteine (**NAC**) also reconstituted the abnormally low concns. of the GSH precursor glutamate in the skeletal muscle tissue of **tumor**-bearing mice. Higher doses, however, enhanced **tumor** growth and increased the plasma glucose level in normal mice. In the latter, cysteine and **NAC** also decreased i.m. catalase and GSH peroxidase activities. Taken together, the studies on the effects of ornithine, cysteine, and **NAC** illuminate some of the mechanistic pathways involved in cachexia and suggest targets for therapeutic intervention.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 19 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:25288 HCAPLUS
DOCUMENT NUMBER: 130:195112
TITLE: Changes in **glutathione** status and the antioxidant system in blood and in **cancer** cells associate with **tumor** growth in vivo
AUTHOR(S): Navarro, Jose; Obrador, Elena; Carretero, Julian; Petschen, Ignacio; Avino, Jose; Perez, Pilar; Estrela, Jose M.
CORPORATE SOURCE: Departamento de Fisiologia, Universidad de Valencia, Facultad de Medicina, Valencia, 46010, Spain
SOURCE: Free Radical Biology & Medicine (**1998**), Volume Date 1999, 26(3/4), 410-418
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relationship among **cancer** growth, the **glutathione** **redox** cycle and the antioxidant system was studied in blood and in **tumor** cells. During **cancer** growth, the **glutathione** **redox** status (GSH/GSSG) decreases in blood of Ehrlich ascites **tumor**-bearing mice. This effect is mainly due to an increase in GSSG levels. Two reasons may explain the increase in blood GSSG: (a) the increase in peroxide production by the **tumor** that, in addition to changes affecting the **glutathione**-related and the antioxidant enzyme activities, can lead to GSH oxidation within the red blood cells; and (b) an increase of GSSG release from different tissues into the blood. GSH and peroxide levels are higher in the **tumor** cells when they **proliferate** actively, however GSSG levels remain constant during **tumor** growth in mice. These changes associate with low levels of lipid peroxidn. in plasma, blood and the **tumor** cells. The GSH/GSSG ratio in blood also decreases in patients bearing breast or colon **cancers** and, as it occurs in **tumor** -bearing mice, this change assocs. with higher GSSG levels, especially in advanced stages of **cancer** progression. Our results indicate that determination of **glutathione** status and oxidative stress-related parameters in blood may help to orientate **cancer** therapy in humans.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 20 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:400616 HCAPLUS

DOCUMENT NUMBER: 129:134396
TITLE: Disruption of **redox** homeostasis in the transforming growth factor-α/c-myc transgenic mouse model of accelerated **hepatocarcinogenesis**
AUTHOR(S): Factor, Valentina M.; Kiss, Andras; Woitach, Joseph T.; Wirth, Peter J.; Thorgeirsson, Snorri S.
CORPORATE SOURCE: Laboratory of Experimental Carcinogenesis, NCI, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Journal of Biological Chemistry (**1998**), 273(25), 15846-15853
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In previous studies the authors have demonstrated that transforming growth factor (TGF)-α/c-myc double transgenic mice exhibit an enhanced rate of cell **proliferation**, accumulate extensive DNA damage, and develop multiple liver **tumors** between 4 and 8 mo of age. To clarify the biochem. events that may be responsible for the genotoxic and **carcinogenic** effects observed in this transgenic model, several parameters of **redox** homeostasis in the liver were examined prior to development of hepatic **tumors.** By 2 mo of age, production of reactive oxygen species, determined by the peroxidn.-sensitive fluorescent dye, 2',7'-dichlorofluorescein diacetate, was significantly elevated in TGF-α/c-myc transgenic hepatocytes vs. either wild type or c-myc single transgenic cells, and occurred in parallel with an increase in lipid peroxidn. Concomitantly with a rise in oxidant levels, antioxidant defenses were decreased, including total **glutathione** content and the activity of **glutathione** peroxidase, whereas **thioredoxin** reductase activity was not changed. However, hepatic **tumors** which developed in TGF-α/c-myc mice exhibited an increase in **thioredoxin** reductase activity and a very low activity of **glutathione** peroxidase. Furthermore, specific deletions were detected in mtDNA as early as 5 wk of age in the transgenic mice. These data provide exptl. evidence that co-expression of TGF-α and c-myc transgenes in mouse liver promotes overprodn. of reactive oxygen species and thus creates an oxidative stress environment. This phenomenon may account for the massive DNA damage and acceleration of **hepatocarcinogenesis** observed in the TGF-α/c-myc mouse model.

REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 21 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:369893 HCAPLUS
DOCUMENT NUMBER: 129:89983
TITLE: Antioxidants reduce cyclooxygenase-2 expression, prostaglandin production, and **proliferation** in colorectal **cancer** cells
AUTHOR(S): Chinery, Rebecca; Beauchamp, R. Daniel; Shyr, Yu; Kirkland, Susan C.; Coffey, Robert J.; Morrow, Jason D.
CORPORATE SOURCE: Department of Medicine, The Vanderbilt Cancer Center, Vanderbilt University Medical Center, Nashville, TN, 37232, USA
SOURCE: Cancer Research (**1998**), 58(11), 2323-2327
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Increased expression of cyclooxygenase (COX) and overprodn. of prostaglandins (PGs) have been implicated in the development and progression of colorectal **cancer** (CRC). Recent observations suggest that reactive oxygen intermediates play a role in **tumor** cell growth regulation and expression of the inducible COX, COX-2. Therefore, the effects of various antioxidants on COX expression and cellular growth were evaluated in the human CRC cell line HCA-7. The antioxidants **pyrrolidinedithiocarbamate** (PDTC), **N-acetylcysteine**, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox), and U74006 decreased PG production, intracellular **redox** status, and cellular growth in a concentration-dependent manner. The decrease in cellular growth was associated with the induction of apoptosis. Unlike the selective COX inhibitors 1-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-5-[(4-fluoro)phenyl]pyrazole (SC 58125) and (2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide (NS 398) that inhibit COX-2 catalytic activity, these antioxidants decreased COX-2 expression at the transcriptional level. Combined treatment of HCA-7 cells with PDTC and SC 58125 resulted in an additive decrease in PG levels and anchorage-dependent and -independent growth. Furthermore, whereas antioxidants or SC 58125 reduced **tumor** growth in vivo, coadministration of PDTC and SC 58125 resulted in actual **tumor** regression. These results suggest that combined therapy with NSAIDs and antioxidants might be useful in the prevention and/or treatment of CRC.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 22 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:229894 HCAPLUS
DOCUMENT NUMBER: 129:234
TITLE: Mechanisms of inhibition of the **thioredoxin** growth factor system by **antitumor** 2-imidazolyl disulfides
AUTHOR(S): Kirkpatrick, D. Lynn; Kuperus, Miles; Dowdeswell, Marla; Potier, Noelle; Donald, Lynda J.; Kunkel, Mark; Berggren, Margareta; Angulo, Miguel; Powis, Garth
CORPORATE SOURCE: Department of Chemistry, University of Regina, Regina, SK, S4S 0A2, Can.
SOURCE: Biochemical Pharmacology (**1998**), 55(7), 987-994
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The interactions of a series of 2-imidazolyl disulfide **antitumor** compds. with the **thioredoxin** reductase (TR)-**thioredoxin** (hTrx) **redox** system have been studied. Bu 2-imidazolyl disulfide (I) and Et 2-imidazolyl disulfide (II) were substrates for reduction by TR with Km values of 43 and 48 μM. 1-Methylpropyl 2-imidazolyl disulfide (III) and benzyl 2-imidazolyl disulfide (IV) were competitive inhibitors of the reduction of hTrx by TR with Ki values of 31 μM. None of the disulfides were substrates for reduction by human **glutathione** reductase. The disulfides caused reversible thioalkylation of hTrx at the **redox** catalytic site as shown by the fact that there was no thioalkylation of a mutant hTrx where both the catalytic site Cys32 and Cys35 residues were replaced by Ser. In addition, the disulfides caused a

slower irreversible inactivation of hTrx as a substrate for reduction by TR, with half-lives for I of 30 min, for III of 4 h, and for tert-Bu 2-imidazolyl disulfide of 24 h. This irreversible inactivation of hTrx occurred at concns. of the disulfides an order of magnitude below those that inhibited TR, and involved the Cys73 of hTrx, which is outside the conserved **redox** catalytic site, as shown by the resistance to inactivation of a mutant hTrx where Cys73 was replaced by Ser. Electrophoretic and mass spectral analyses of the products of the reaction between the disulfides and hTrx show that modification of 1-3 Cys residues of the protein occurred in a concentration-dependent fashion. The disulfides inhibited the hTrx-dependent **proliferation** of MCF-7 breast **cancer** cells with IC50 values of I and III of 0.2 and 1.2 μM, resp. The results show that although the catalytic sites of TR and hTrx are reversibly inhibited by the 2-imidazolyl disulfides, it is the irreversible thioalkylation of Cys73 of hTrx by the disulfides that most probably accounts for the inhibition of **thioredoxin**-dependent cell grown by the disulfides.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 23 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:163492 HCAPLUS
DOCUMENT NUMBER: 128:213410
TITLE: Modulators of nitrosative and oxidative stress for the treatment of disease
INVENTOR(S): Stamler, Jonathan S.; Griffith, Owen W.
PATENT ASSIGNEE(S): Duke University, USA; Medical College of Wisconsin Research Foundation, Inc.
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 9808566 | A1 | 19980305 | WO 1997-US13876 | | 19970813 <-- |
| W: AU, CA, JP | | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | | |
| US 6057367 | A | 20000502 | US 1997-852490 | | 19970507 <-- |
| CA 2262708 | AA | 19980305 | CA 1997-2262708 | | 19970813 <-- |
| AU 9740542 | A1 | 19980319 | AU 1997-40542 | | 19970813 <-- |
| EP 963219 | A1 | 19991215 | EP 1997-938149 | | 19970813 <-- |
| R: CH, DE, ES, FR, GB, IT, LI, NL, SE | | | | | |
| US 6180824 | B1 | 20010130 | US 1999-361167 | | 19990727 <-- |
| US 6359004 | B1 | 20020319 | US 2000-690989 | | 20001018 <-- |
| US 2003096870 | A1 | 20030522 | US 2001-13455 | | 20011213 <-- |
| US 6608110 | B2 | 20030819 | | | |
| US 2003207815 | A1 | 20031106 | US 2003-417238 | | 20030417 <-- |
| PRIORITY APPLN. INFO.: | | | US 1996-25819P | P | 19960830 <-- |
| | | | US 1997-852490 | A | 19970507 <-- |
| | | | WO 1997-US13876 | W | 19970813 <-- |
| | | | US 1999-361167 | A1 | 19990727 |
| | | | US 2000-690989 | A1 | 20001018 |
| | | | US 2001-13455 | A3 | 20011213 |

AB Mammals are treated for infections or for conditions associated with pathol. **proliferating** mammalian cell growth (for example, certain **cancers**, restenosis, benign prostatic hypertrophy) by

administration of a manipulator of nitrosative stress to selectively kill or reduce the growth of the microbes or helminths causing the infection or of host cells infected with the microbes or of the pathol. **proliferating** mammalian cells. Novel agents include α-alkyl-S-alkyl-homocysteine sulfoximines wherein the α-alkyl contains 2-8 carbon atoms, and the S-alkyl contains 1-10 carbon atoms. In another invention herein, mammals in need of increased nitrosative stress defenses are treated, e.g. humans at risk for a stroke because of having had a transient ischemic attack are treated. Treatments to increase nitrosative stress defenses include, for example, repeated administrations of low doses of manipulators of nitrosative stress so that the subject treated has increased tolerance to nitrosative stress. In still another invention, mammals are treated for protozoal infections by systemic administration of L-buthionine-S-sulfoximine and agent that increases nitrosative stress.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 24 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:84114 HCAPLUS
DOCUMENT NUMBER: 128:179261
TITLE: **Thiol redox** modulation of **tumor** necrosis factor-α responsiveness in cultured AIDS-related Kaposi's sarcoma cells
AUTHOR(S): Mallery, S. R.; Landwehr, D. J.; Ness, G. M.; Clark, Y. M.; Hohl, C. M.
CORPORATE SOURCE: Departments of Oral Surgery and Pathology, Colleges of Dentistry and Medicine, Ohio State University, Columbus, OH, 43210, USA
SOURCE: Journal of Cellular Biochemistry (**1998**), 68(3), 339-354
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Both clin. and exptl. evidence indicates that AIDS-related Kaposi's sarcoma (AIDS-KS) has a multifactorial pathogenesis with factors such as HIV viral load, latent virus induction, and opportunistic infections contributing to disease progression. However, a consistent feature that unites these apparently diverse putative etiol. agents is sustained serum elevations of pro-inflammatory cytokines such as **tumor** necrosis factor-α (TNF-α). While virtually every cell responds to TNF-α with gene activation, the extent of TNF-α-mediated cellular signaling is regulated by a delicate balance between signal activation and signal arresting events. Reactive oxygen intermediates (ROI), which are generated as a consequence of TNF-α membrane interaction, are part of this TNF-α-initiated cellular activation cascade. Previous studies in the authors' laboratory have shown that AIDS-KS cells possess impaired oxygen intermediate scavenging capacities, thereby establishing conditions permissive for the intracellular retention of ROI. Here, the authors used cellular capacity to upregulate the cytoprotective enzyme superoxide dismutase (SOD) to address the extent of cellular response to TNF-α. Concurrent with the SOD analyses, nucleotide profiles were obtained to assess cellular bioenergetic responses during TNF-α challenge. **Proliferative** growth levels of mitochondrial (Mn)SOD activities showed an activity spectrum ranging from lowest activity in AIDS-KS cells, to intermediate levels in matched, nonlesional cells from the AIDS-KS donors, to highest activities in HIV normal fibroblasts. In contrast, following TNF-α challenge, the

AIDS-KS and KS donor nonlesional cells showed a 11.89- and 5.86-fold resp. increase in MnSOD activity, while the normal fibroblasts demonstrated a 1.35-fold decrease. Subsequent **thiol redox** modulation studies showed that only the normal fibroblast cultures showed a potentiation of TNF-α-mediated MnSOD upregulation following GSH depletion. In addition, provision of the GSH precursor, **N-acetylcysteine** during TNF-α challenge only diminished MnSOD activity and mitochondrial compartmentalization in the AIDS-KS cells, a finding that likely reflects the lower levels of reduced **thiols** in this cellular population. The authors' data, which show that a perturbation in their cellular **thiol redox** status accentuates AIDS-KS cellular responsiveness to TNF-α, suggest a biochem. rationale for the recognized TNF-α AIDS-KS clin. correlation.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 25 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:49693 HCAPLUS
DOCUMENT NUMBER: 128:149308
TITLE: Cellular **thioredoxin** reductase activity is regulated by selenium
AUTHOR(S): Berggren, Margareta; Gallegos, Alfred; Gasdaska, John; Powis, Garth
CORPORATE SOURCE: Arizona Cancer Center, University of Arizona Health Sciences Center, Tucson, AZ, 85724-5024, USA
SOURCE: Anticancer Research (**1997**), 17(5A), 3377-3380
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Selenium (Se) is an essential trace element and has been reported to decrease the incidence of some human **cancers.** The authors have investigated the effects of Se on **thioredoxin** reductase, a selenocysteine containing flavoenzyme, in HT-29 human colon **cancer** cells grown in serum-free medium. Sodium selenite and other Se containing compds. produced a time and concentration dependent increase in intracellular **thioredoxin** reductase activity and protein levels. Selenite was the most active of the Se compds. examined: 1 μM selenite produced a 28-fold increase in **thioredoxin** reductase activity by 1 day and 10 μM selenite over a 60-fold increase by 5 days. The activity of a related non-selenocysteine containing flavoenzyme **glutathione** reductase was not increased by selenite. Selenite, but not the other Se containing compds. inhibited cell growth at concns. above 2 μM. The results show that Se can produce large increases in cell **thioredoxin** reductase activity.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 26 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:729411 HCAPLUS
DOCUMENT NUMBER: 128:21764
TITLE: Role of intracellular **redox** status in apoptosis induction of human T-cell leukemia virus type I-infected lymphocytes by 13-cis-retinoic acid
AUTHOR(S): Furuke, Keizo; Sasada, Tetsuro; Ueda-Taniguchi, Yasuyo; Yamauchi, Akira; Inamoto, Takashi; Yamaoka, Yoshio; Masutani, Hiroshi; Yodoi, Junji

CORPORATE SOURCE: Department of Biological Responses, Institute for Virus Research, Kyoto University, Kyoto, 606-01, Japan
SOURCE: Cancer Research (**1997**), 57(21), 4916-4923
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have shown that cell cycle progression of human T-cell leukemia virus type I (HTLV-I)-transformed T-cell lines was inhibited by 13-cis-retinoic acid (13cRA). In the present study, we report that 13cRA inhibited **proliferation** and induced cell death of peripheral blood mononuclear cells obtained from four patients with acute adult T-cell leukemia but not of mitogen- or interleukin 2-activated peripheral blood mononuclear cells from HTLV-I-neg. healthy donors. Because HTLV-I-infected lymphocytes are susceptible to oxidative stress, we examined the role of the intracellular **redox** state in 13cRA-induced cell death using a HTLV-I-pos. T-cell line, ATL2, as a model. The 13cRA induced apoptosis in ATL2 cells within 48 h in a dose-dependent manner. The ability of 13cRA to induce apoptosis was more potent than that of all-trans-retinoic acid. Apoptosis induction by 13cRA was significantly enhanced by **buthionine sulfoximine** (BSO), which decreased the levels of intracellular reduced **glutathione**, although 13cRA by itself did not alter them, suggesting that intracellular reduced **glutathione** may modulate 13cRA-induced apoptosis. In addition, flow cytometric anal. revealed that 13cRA increased intracellular peroxides in 24 h and that the addition of BSO further enhanced them. Although **N-acetylcysteine** had only a marginal effect, pretreatment with catalase markedly inhibited 13cRA-induced apoptosis. These results suggest that peroxide generation, i.e., oxidative stress, may play a crucial role in the induction of apoptosis by 13cRA and further demonstrate that combined treatment with 13cRA and BSO induces apoptosis of HTLV-I-pos. lymphocytes even more potently.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 27 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:561551 HCAPLUS
DOCUMENT NUMBER: 127:218945
TITLE: Nitric oxide and superoxide induced p53 and Bax accumulation during mesangial cell apoptosis
AUTHOR(S): Sandau, Katrin; Pfeilschifter, Josef; Brune, Bernhard
CORPORATE SOURCE: Faculty of Medicine, Department of Medicine IV, Experimental Division, University of Erlangen-Nurnberg, Erlangen, Germany
SOURCE: Kidney International (**1997**), 52(2), 378-386
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB During **proliferative** glomerulonephritis, the early phase of mesangiolysis is linked to increased nitric oxide (NO) production NO as well as superoxide (O2-) are inflammatory mediators that are generated by mesangial cells (MC) after cytokine stimulation. Added individually, both radicals induce MC apoptosis. However, the coexistence of a defined NO/O2- ratio is cross-protective. Apoptosis is characterized by specific features such as chromatin condensation, DNA strand breaks, and the occurrence of apoptotic regulating proteins. The **tumor** suppressor p53 and Bax (Bcl-2 associated protein x) are considered to be classical death promoters, which accumulate after toxic insults. To study

p53 and Bax protein accumulation in NO and/or O2--induced apoptosis, the authors used the NO-donor S-**nitrosoglutathione** (GSNO) and the **redox** cycler 2,3-dimethoxy-1,4-naphthoquinone (DMNQ). Both agonists initiated DNA fragmentation in a concentration dependent manner associated with transient p53 and Bax up-regulation. Co-generation of NO/O2- resulted not only in reduced DNA fragmentation, but also in decreased Bax accumulation. Comparable to the NO/O2- co-generation, cytokines failed to induce apoptosis. In contrast, cytokines in combination with pyrrolidine **dithiocarbamate**, which blocks endogenous superoxide dismutase, allowed p53 and Bax accumulation as well as DNA fragmentation. The results demonstrate p53 and Bax as early components in NO and O2--induced rat MC apoptosis and point to the NO/O2- interaction as a naturally occurring cell defense mechanism.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 28 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:556476 HCAPLUS
DOCUMENT NUMBER: 127:275947
TITLE: Generation of angiostatin by reduction and proteolysis of plasmin. Catalysis by a plasmin reductase secreted by cultured cells
AUTHOR(S): Stathakis, Paul; Fitzgerald, Melinda; Matthias, Lisa J.; Chesterman, Colin N.; Hogg, Philip J.
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, School of Pathology and Department of Haematology, Prince of Wales Hospital, University of New South Wales, Sydney, NSW 2052, Australia
SOURCE: Journal of Biological Chemistry (**1997**), 272(33), 20641-20645
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Extracellular manipulation of protein disulfide bonds has been implied in diverse biol. processes, including penetration of viruses and endotoxin into cells and activation of certain cytokine receptors. We now demonstrate reduction of one or more disulfide bonds in the serine proteinase, plasmin, by a reductase secreted by Chinese hamster ovary or HT1080 cells. Reduction of plasmin disulfide bond(s) triggered proteolysis of the enzyme, generating fragments with the domain structure of the angiogenesis inhibitor, angiostatin. Two of the known reductases secreted by cultured cells are protein disulfide isomerase and **thioredoxin**, and incubation of plasmin with these purified reductases resulted in angiostatin fragments comparable with those generated from plasmin in cell culture. **Thioredoxin**-derived angiostatin inhibited **proliferation** of human dermal microvascular endothelial cells with half-maximal effect at approx. 0.2 μg/mL. Angiostatin made by cells and by purified reductases contained free sulfhydryl group(s), and S-carbamidomethylation of these **thiol** group(s) ablated biol. activity. Neither protein disulfide isomerase nor **thioredoxin** were the reductases used by cultured cells, because immunodepletion of conditioned medium of these proteins did not affect angiostatin generating activity. The plasmin reductase secreted by HT1080 cells required a small cofactor for activity, and physiol. relevant concns. of reduced **glutathione** fulfilled this role. These results have consequences for plasmin activity and angiogenesis, particularly in the context of

**tumor** growth and metastasis. Moreover, this is the first demonstration of extracellular reduction of a protein disulfide bond, which has general implications for cell biol.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 29 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:511962 HCAPLUS
DOCUMENT NUMBER: 127:117382
TITLE: Oxidized **glutathione**, salts, and derivatives as enhancers of endogenous production of cytokines and hemopoietic factors, and methods of therapeutic use
INVENTOR(S): Balazovsky, Mark Borisovich; Kozhemyakin, Leonid Andreevich
PATENT ASSIGNEE(S): Balazovsky, Mark Borisovich, Russia; Kozhemyakin, Leonid Andreevich
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 9721444 | A1 | 19970619 | WO 1996-RU340 | | 19961210 <-- |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | | |
| RU 2089179 | C1 | 19970910 | RU 1995-120403 | | 19951214 <-- |
| WO 9721443 | A1 | 19970619 | WO 1996-RU226 | | 19960808 <-- |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | | |
| AP 928 | A | 20010115 | AP 1998-1260 | | 19961201 <-- |
| W: KE, LS, MW, SD, SZ, UG | | | | | |
| AU 9711130 | A1 | 19970703 | AU 1997-11130 | | 19961210 <-- |
| EP 869809 | A1 | 19981014 | EP 1996-941915 | | 19961210 <-- |
| EP 869809 | B1 | 20020327 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | | |
| RU 2153351 | C2 | 20000727 | RU 1998-108088 | | 19961210 <-- |
| JP 2000515111 | T2 | 20001114 | JP 1997-521965 | | 19961210 <-- |
| AT 214936 | E | 20020415 | AT 1996-941915 | | 19961210 <-- |
| US 6492329 | B1 | 20021210 | US 2000-702701 | | 20001031 <-- |
| PRIORITY APPLN. INFO.: | | | RU 1995-120403 | A | 19951214 <-- |
| | | | WO 1996-RU226 | A | 19960808 <-- |
| | | | US 1996-733886 | A | 19961018 <-- |
| | | | WO 1996-RU340 | A | 19961210 <-- |

US 1996-766557 A 19961211 <--

AB A method for stimulating endogenous production of cytokines and hemopoietic factors comprises topical or parenteral administration of an effective amount of oxidized **glutathione**, and/or a pharmaceutically acceptable salt and/or derivative thereof, for a period sufficient to stimulate the endogenous production to obtain a therapeutic effect. The oxidized **glutathione** and/or pharmaceutically acceptable salt and/or derivative is introduced along with an extender of their half life. The compds. of the invention may be used in the treatment of **neoplasms**, immune diseases, etc.

L36 ANSWER 30 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:350237 HCAPLUS
DOCUMENT NUMBER: 127:13137
TITLE: Retinoid induces growth inhibition of adult T-cell leukemia cells
AUTHOR(S): Miyatake, Jun-Ichi; Maeda, Yasuhiro
CORPORATE SOURCE: Third Department of Internal Medicine, Kinki University School of Medicine, Osakasayama, 589, Japan
SOURCE: Acta Medica Kinki University (**1997**), 22(1), 111-121
CODEN: AMKUDT; ISSN: 0386-6092
PUBLISHER: Kinki University Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of retinoic acid (RA) on the cell growth and expression of interleukin-2 (IL-2) receptor (IL-2Rα/p55, Tac, CD25) by the human T lymphotropic virus type I pos. (HTLV-I(+)) T cell lines, HUT102 and ATL-2, were investigated. Incubation of these cells with RA resulted in marked growth inhibition and down-regulation of CD25 expression. Four clones of HUT102 cell lines were established by limiting dilution, and RA was shown to inhibit the growth and CD25 expression in three of these clones, but in the fourth. However, RA did not induce growth inhibition of the HTLV-I-neg. T cell lines, MOLT-4 and Jurkat, and of normal lymphocytes that had been stimulated with phytohemagglutinin. We hypothesized that the sensitivity to retinoids depends on an imbalance in intracellular **redox** potential. To examine the effect of exogenous **thiol** compds. for the growth inhibition of HTLV-I(+) T cell lines induced by RA, these cell lines were cultured with several **thiol** compds. (ATL-derived factor, **thioredoxin**, L-cystine and **glutathione** (GSH)), following the addition of RA in **thiol** -free medium. Unexpectedly, **thiol** compds. alone, when added after RA, did not restore the growth inhibition of HTLV-I(+) T cell lines induced by RA. However, when those cells were preincubated with **thiol** compds. for 24 h, no RA-induced growth inhibition was observed These findings suggest that intracellular reductive environments induced by **thiol** compds. are associated with resistance to RA of HTLV-I(+) T cells, and that **thiol** compds. may play an important role in HTLV-I(+) T cell **proliferation.**

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 31 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:153170 HCAPLUS
DOCUMENT NUMBER: 126:223448
TITLE: Decreased activity of inducible nitric oxide synthase type 2 and modulation of the expression of **glutathione** S-transferase α, bcl-2, and metallothioneins during the differentiation of CaCo-2

cells
AUTHOR(S): Vecchini, Francoise; Pringault, Eric; Billiar, Timothy R.; Geller, David A.; Hausel, Pierrette; Felley-Bosco, Emanuela
CORPORATE SOURCE: Institut de Pharmacologie et Toxicologie, Lausanne, 1005, Switz.
SOURCE: Cell Growth & Differentiation (**1997**), 8(2), 261-268
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Reactive oxygen species modulate the cell growth of a wide variety of mammalian cells. To determine whether oxidative metabolism is altered during the differentiation process, we studied the expression of pro- and antioxidant proteins in **proliferating** and differentiated CaCo-2 cells, a human colon **adenocarcinoma** cell line. Nitric oxide synthase type 2 (iNOS) produces nitric oxide (NO). Depending on its rate of synthesis, NO may either promote cellular and DNA damage or reduce the ability of other free radicals to induce cell injury. Using Western and Northern blot anal. and arginine conversion assay, we demonstrate that the expression of iNOS decreases when cells undergo differentiation. This biol. event entails a diminished production of NO metabolites and correlates with the loss of activation of soluble guanylate cyclase activity. In differentiated cells, a 2-fold down-regulation of the nuclear factor kB activity was observed, suggesting that nuclear factor kB could be one of the iNOS gene regulatory factors in the CaCo-2 model. In parallel, we studied the expression of other antioxidant proteins including **glutathione** S-transferase α (GSTα), bcl-2, and the metallothioneins (MTs). We show that the protein levels of GSTα and MT increase during the differentiation of CaCo-2 cells, whereas bcl-2 levels decrease. Our investigation indicates that the expression of iNOS, GSTα, bcl-2, and MT is associated with the enterocytic differentiation. The shift in the expression of specific antioxidant genes during CaCo-2 cell differentiation may occur to avoid alterations in the cell **redox** potential.

L36 ANSWER 32 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:21606 HCAPLUS
DOCUMENT NUMBER: 126:152441
TITLE: Induction of p21 mediated by reactive oxygen species formed during the metabolism of aziridinylbenzoquinones by HCT116 cells
AUTHOR(S): Qiu, Xiaobo; Forman, Henry Jay; Schoenthal, Axel H.; Cadenas, Enrique
CORPORATE SOURCE: Sch. Pharm., Univ. Southern California, Los Angeles, CA, 90033, USA
SOURCE: Journal of Biological Chemistry (**1996**), 271(50), 31915-31921
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aziridinylbenzoquinones are a group of **antitumor** agents that elicit cytotoxicity by generating either alkylating intermediates or reactive oxygen species. The mechanism of toxicity may not always, however, involve profound damage of cellular constituents, but may involve

a cytostatic effect through interference with the cell cycle. In this context, the authors have examined the induction of the cell cycle inhibitor p21 (WAF1, CIP1, or sdi1), whose overexpression suppresses the growth of various **tumor** cells, in human **tumor** cells metabolizing 3,6-diaziridinyl-1,4-benzoquinone (DZQ) and its C2,C5-substituted derivs.: 2,5-bis-(carboethoxyamino) (AZQ) and 2,5-bis-(2-hydroxyethylamino) (BZQ). Both DZQ and AZQ were effectively activated by HCT116 human colonic **carcinoma** cells; the activation of the former involved largely a dicoumarol-sensitive activity, whereas that of the latter appeared to be accomplished primarily by one-electron transfer reductases. BZQ was not a substrate for the dicoumarol-sensitive enzyme in HCT116 cells. Cellular activation of the first two quinones was associated with formation of oxygen-centered radicals as detected by EPR in conjunction with the spin trap 5,5'-dimethyl-1-pyrroline-N-oxide. The **redox** transitions of DZQ involved hydroxyl radical formation and were strongly inhibited by catalase, whereas those of AZQ showed a strong superoxide anion component sensitive to superoxide dismutase. These signals were suppressed by **N-acetylcysteine** with concomitant production of a thiyl radical adduct. This suggests an effective electron transfer between the **thiol** and free radicals formed during the activation of these quinones. DZQ and AZQ induced significantly the expression of p21 in HCT116 cells, but a 10-fold higher concentration of AZQ was required to achieve the level of induction elicited by DZQ. BZQ had little effect on p21 expression. P21 induction at both mRNA and protein levels correlated with the inhibition of either cyclin-dependent kinase activity or cell **proliferation.** P21 induction elicited by the above quinones was inhibited by **N-acetylcysteine**, whereas the non-sulfur analog, N-acetylalanine, was without effect. Catalase and superoxide dismutase did not effect p21 induction by aziridinylbenzoquinones in HCT116 cells, thus suggesting that extracellular sources of oxygen radicals generated by plasma membrane reductases have no influence in the expression of this gene. Hydrogen peroxide, a product of quinone **redox** cycling, elicited an increase of p21 mRNA levels in HCT116 and K562 human chronic myelogenous leukemia cells. The latter lacks p53, one of the activators of p21 transcription, thus suggesting that p21 expression can be accomplished in a p53-independent manner in these cells. This study suggests that p21 induction is mediated by an increase in the cellular steady-state concentration of oxygen radicals and that the greater effectiveness in p21 induction by DZQ may be related to its efficient metabolism by NAD(P)H:quinone oxidoreductase activity in HCT116 cells.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 33 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:936 HCAPLUS
DOCUMENT NUMBER: 126:84934
TITLE: Melatonin and oncostatic signal transduction: evidence for a novel mechanism involving **glutathione** and nitric oxide
AUTHOR(S): Blask, David E.; Wilson, Sean T.
CORPORATE SOURCE: Mary Imogene Bassett Hosp., Res. Inst., Cooperstown, NY, 13326-1394, USA
SOURCE: Advances in Pineal Research (**1994**), 8, 465-471
CODEN: APIREW; ISSN: 0269-0071
PUBLISHER: Libbey
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Melatonin is a unique neurohormone that has many diverse functions in

addition to its well-known role in biol. timekeeping. One of these functions is its ability to inhibit the promotion of **tumor** growth in vivo and in vitro, particularly of breast **cancer** cells. However, virtually nothing is known with respect to potential signal transduction pathways that may mediate melatonin's oncostatic action at the cellular level. Since one mechanism of **tumor** promotion may involve a prooxidant state of **cancer** cells, the authors have examined the role of the intracellular **redox** state in melatonin's mechanism of action in MCF-7 human breast **cancer** cells in vitro. Specifically, the authors report new evidence for a novel signal transduction mechanism mediating melatonin's oncostatic action involving the endogenous antioxidant **glutathione** (GSH) and a free radical species and newly discovered intracellular messenger mol., nitric oxide (NO). When the synthesis of either GSH or NO is inhibited, melatonin no longer exerts its **antiproliferative** effect, suggesting that these mols. play a critical role in transmitting melatonin's oncostatic message within breast **cancer** cells.

L36 ANSWER 34 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:756018 HCAPLUS
DOCUMENT NUMBER: 126:87554
TITLE: Oxidative inactivation of **thioredoxin** as a cellular growth factor and protection by a Cys73 → Ser mutation
AUTHOR(S): Gasdaska, John R.; Kirkpatrick, D. Lynn; Montfort, William; Kuperus, Miles; Hill, Simon R.; Berggren, Margareta; Powis, Garth
CORPORATE SOURCE: Arizona Cancer Center, Univ. Arizona Health Services Center, Tucson, AZ, 85724-5024, USA
SOURCE: Biochemical Pharmacology (**1996**), 52(11), 1741-1747
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Thioredoxin** (Trx) is a widely distributed **redox** protein that regulates several intracellular **redox**-dependent processes and stimulates the **proliferation** of both normal and **tumor** cells. We have found that when stored in the absence of reducing agents, human recombinant Trx undergoes spontaneous oxidation, losing its ability to stimulate cell growth, but is still a substrate for NADPH-dependent reduction by human **thioredoxin** reductase. There is a slower spontaneous conversion of Trx to a homodimer that is not a substrate for reduction by **thioredoxin** reductase and that does not stimulate cell **proliferation.** Both conversions can be induced by chemical oxidants and are reversible by treatment with the **thiol** reducing agent **dithiothreitol.** SDS-PAGE suggests that Trx undergoes oxidation to monomeric form(s) preceding dimer formation. We have recently shown by X-ray crystallog. that Trx forms a dimer that is stabilized by an intermol. Cys73-Cys73 disulfide bond. A Cys73 → Ser mutant Trx (C73S) was prepared to determine the role of Cys73 in oxidative stability and growth stimulation. C73S was as effective as Trx in stimulating cell growth and was a comparable substrate for **thioredoxin** reductase. C73S did not show spontaneous or oxidant-induced loss of activity and did not form a dimer. The results suggest that Trx can exist in monomeric forms, some of which are mediated by Cys73 that do not stimulate cell **proliferation** but can be reduced by **thioredoxin** reductase. Cys73 is also involved in formation of an enzymically inactive homodimer, which occurs on long term

storage or by chemical oxidation Thus, although clearly involved in protein inactivation, Cys73 is not necessary for the growth stimulating activity of Trx.

L36 ANSWER 35 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:608659 HCAPLUS
DOCUMENT NUMBER: 125:271948
TITLE: Selenite and selenate inhibit human lymphocyte growth via different mechanisms
AUTHOR(S): Spyrou, Giannis; Bjoernstedt, Mikael; Skog, Sven; Homgren, Arne
CORPORATE SOURCE: Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, S-171 77, Swed.
SOURCE: Cancer Research (**1996**), 56(19), 4407-4412
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Selenium compds. like selenite and selenate have strong inhibitory effects, particularly on mammalian **tumor** cell growth by unknown mechanisms. We found that the addition of sodium selenite and sodium selenate inhibited the growth of human 3B6 and BL41 lymphocytes. Selenite was more potent because 10 μM selenite produced a growth inhibitory effect similar to that of 250 μM selenate. The mechanism of action of selenite and selenate appears to be different. 3B6 and BL41 cells treated with selenite accumulated in the S-phase; however, selenate caused an accumulation of cells in G2. Selenite-mediated growth inhibition was irreversible, although the effects of selenate could be reversed. Selenite, in contrast to selenate, is efficiently reduced by the **thioredoxin** system (**thioredoxin**, **thioredoxin** reductase, and NADPH). At concns. required to observe a similar effect on cell growth, the activity of **thioredoxin** reductase, recently shown to be a selenoprotein, increased in selenite-treated cells and decreased in selenate-treated cells. Ribonucleotide reductase activity was inhibited in an in vitro assay by selenite and **selenodiglutathione** but not by selenate. These results show that selenite and selenate use different mechanisms to inhibit cell growth.

L36 ANSWER 36 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:263007 HCAPLUS
DOCUMENT NUMBER: 124:314095
TITLE: Reduction-oxidation (**redox**) state regulation of extracellular matrix metalloproteinases and tissue inhibitors in cardiac normal and transformed fibroblast cells
AUTHOR(S): Tyagi, Suresh C.; G. Suresh Kumar; Borders, Susan
CORPORATE SOURCE: Dalton Cardiovascular Research Center, University Missouri-Columbia, Columbia, MO, 65212, USA
SOURCE: Journal of Cellular Biochemistry (**1996**), 61(1), 139-51
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Latent matrix metalloproteinases (MMPs) in normal myocardium are activated in end-stage heart failure. In vitro oxidized **glutathione** (GSSG) activates myocardial MMPs which contains a cysteine residue. In vivo GSSG induce the collagen lysis and cardiac dilatation. To assess whether **thiol** and non-**thiol** reducing agents have

direct effect on the interstitial human heart fibroblast (HHF) **proliferation** and MMP expression, HHF and polyoma virus transformed fibroblast cells were cultured with or without the **thiol**-containing reduced (GSH) or oxidized (GSSG) **glutathiones**, pyrrolidine **dithiocarbamate** (PDTC) and N-acetylcysteilne (**NAC**), and non-**thiol** ascorbic acid. After 100 μg/mL (.apprx.0.3 mM) GSH or PDTC treatment the **proliferative** (synthetic) phenotype of transformed fibroblast cells was changed to quiescent (contractile) phenotype. Also, after GSH, PDTC, and ascorbic acid treatment the medium was then analyzed for MMP activity by zymog. The results indicate reduction in MMP expression in transformed fibroblast cells after GSH and PDTC treatments and no effect after ascorbic acid treatment. Based on reverse zymog., we observed the level of tissue inhibitor of metalloproteinase (TIMP) at a decreased level in transformed cells. The effect of the reducing agent at the gene transcription was measured by estimating mRNA (Northern blot anal.) of MMP and of TIMP in the cells that were cultured in medium in the presence and absence of GSH. These results indicate that GSH induces MMP-2 and MMP-1 expression in normal HHF and that GSH reduces MMP-2 and MMP-1 in transformed fibroblast cells. After the treatment, the TIMP-2 level was repressed in normal HHF and TIMP-2 level increased in transformed fibroblast cells. These events are dependent on the nuclear transcription factor activity on the collagenase promoter in normal HHF cells. On the other hand, in polyoma transform fibroblast cells these events are not dependent on this collagenase promoter. These results suggest that oxidative environment induces normal HHF cell **proliferation**, and the reducing agent decreases normal HHF cell **proliferation** by inducing MMP and repressing TIMP gene transcription. In transformed cells reducing agents inhibit MMP expression and increase TIMP levels, which suggests a role of antioxidants in preventing **tumorigenesis.**

L36 ANSWER 37 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:205604 HCAPLUS
DOCUMENT NUMBER: 124:313432
TITLE: **Redox** changes in normal and **neoplastic** cells during the cell cycle. I. Bioreduction of nitroxides by CHO cells with different mitotic activity
AUTHOR(S): Panz, Tadeusz
CORPORATE SOURCE: Institute Molecular Biology, Jagiellonian University, Krakow, Pol.
SOURCE: Current Topics in Biophysics (**1994**), 18(2), 112-16
CODEN: CTOBEU; ISSN: 1232-9630
PUBLISHER: Wydawnictwo Protext
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chinese Hamster Ovary (CHO) cells cultured in vitro and isolated in logarithmic phase of growth reduced spin probes at a lower rates than cells isolated during plateau phase of growth. This phenomenon was observed for nitroxides located in cell membranes and those penetrating into the cells. Blocking of electron transport in mitochondria with inhibitors slowed down the bioredn., whereas uncoupling of mitochondrial phosphorylation increased the rate of this process.

L36 ANSWER 38 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:170826 HCAPLUS
DOCUMENT NUMBER: 124:220550
TITLE: Treatment for atherosclerosis and other cardiovascular

and inflammatory diseases with dithiocarboxylates and **dithiocarbamates** which block VCAM-1 expression
INVENTOR(S): Medford, Russell M.; Alexander, R. Wayne; Parthasarathy, Sampath; Khan, Bobby V.; Offermann, Margaret K.
PATENT ASSIGNEE(S): Emory University, USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9530415 | A1 | 19951116 | WO 1995-US5880 | 19950510 <-- |
| W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UZ, VN | | | | |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5807884 | A | 19980915 | US 1994-317399 | 19941004 <-- |
| AU 9525860 | A1 | 19951129 | AU 1995-25860 | 19950510 <-- |
| AU 709939 | B2 | 19990909 | | |
| EP 759752 | A1 | 19970305 | EP 1995-920396 | 19950510 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| BR 9507716 | A | 19970923 | BR 1995-7716 | 19950510 <-- |
| JP 10500111 | T2 | 19980106 | JP 1995-529200 | 19950510 <-- |
| JP 3120091 | B2 | 20001225 | | |
| PL 180874 | B1 | 20010430 | PL 1995-317193 | 19950510 <-- |
| NZ 287214 | A | 20010525 | NZ 1995-287214 | 19950510 <-- |
| PL 184466 | B1 | 20021129 | PL 1995-342067 | 19950510 <-- |
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| NO 9604742 | A | 19961108 | NO 1996-4742 | 19961108 <-- |
| AU 9937951 | A1 | 19990902 | AU 1999-37951 | 19990702 <-- |
| AU 733198 | B2 | 20010510 | | |

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| PRIORITY APPLN. INFO.: | US 1994-240858 | A | 19940510 <-- |
| | US 1994-317399 | A | 19941004 <-- |
| | US 1992-969934 | A2 | 19921030 <-- |
| | AU 1994-56653 | A3 | 19931101 <-- |
| | AU 1995-25860 | A3 | 19950510 <-- |
| | WO 1995-US5880 | W | 19950510 <-- |

OTHER SOURCE(S): MARPAT 124:220550
AB Dithiocarboxylates, including **dithiocarbamates**, block the induced expression of the endothelial cell surface adhesion mol. VCAM-1, and are therefore useful in the treatment of cardiovascular disease, including atherosclerosis, as well as noncardiovascular inflammatory diseases that are mediated by VCAM-1. Identification of oxidized and unoxidized polyunsatd. fatty acids as direct mediators of VCAM-1 expression is described.

L36 ANSWER 39 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:46443 HCAPLUS
DOCUMENT NUMBER: 124:169927
TITLE: Identification of proteins that are abnormally regulated in differentiated cultured human keratinocytes
AUTHOR(S): Olsen, Eydfinnur; Rasmussen, Hanne Holm; Celis, Julio

E.
CORPORATE SOURCE: Dep. Medical Biochem., Aarhus Univ., Aarhus, Den.
SOURCE: Electrophoresis (**1995**), 16(12), 2241-8
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Comparison of the protein expression patterns of **proliferating** normal primary human keratinocytes plated in serum-free medium (SFKM) supplemented with epidermal growth factor (EGF) and bovine pituitary extract (BPE), and similar cultures induced to differentiate by the addition of Dulbecco's modified Eagle medium (DMEM), containing 10% fetal calf serum (FCS) revealed several known and unknown polypeptides that are abnormally regulated in the differentiated cells. Upregulated proteins included keratins (keratin 6, 10/11, 14 and 16), members of the S100 protein family (psoriasin, MRP8, MRP14 and S100c), actin-binding proteins (gelsolin and tropomyosin 9220), annexins (annexins IV and VIII), hsp28, the fatty acid binding protein 5 (FABP5) the squamous cell **carcinoma** (SCC) antigen, members of the 14-3-3 family, involucrin, E-cadherin, cystatin A, desmoglein and integrins α2 and β1, as well as several proteins of as yet unknown identity. The highest upregulated proteins correspond to psoriasin (124.0 times), MRP8 (42.4 times), MRP14 (14.9 times), tropomyosin 9220 (11.5 times), involucrin (11.1 times), and FABP5 (9.1 times). FABP5, hsp28, and tropomyosin 9220 were also highly upregulated in quiescent keratinocytes indicating that their increased levels in the differentiated cells may be due to loss of **proliferative** activity. Highly downregulated proteins included PAI-2, tropomyosins 9213, 9121 and 9122, keratin 5, calnexin, 14-3-3 beta and eta, nucleoside diphosphate kinase A, Rho GDIs, hsp60, hnRNPs H and C2, α-enolase, eIF-4D, **thioredoxin**, annexins III and V, moesin, nucleolar protein B23, GST π and PCNA/cyclin. Both the high expression of keratin 6 and 16, which are markers for an alternative pathway of keratinocyte differentiation, as well as the extremely high upregulation of some members of the S100 protein family indicate that the cells differentiated via an abnormal pathway.

L36 ANSWER 40 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:28756 HCAPLUS
DOCUMENT NUMBER: 124:78608
TITLE: The organization of the human GSTP1-1 gene promoter and its response to retinoic acid and cellular **redox** status
AUTHOR(S): Xia, Chulin; Hu, Jiangting; Ketterer, Brian; Taylor, John B.
CORPORATE SOURCE: Department Biochemistry Molecular Biology, University College London, London, W1P 6DB, UK
SOURCE: Biochemical Journal (**1996**), 313(1), 155-61
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB High levels of expression of GSTP1-1 are associated with cell **proliferation**, embryogenesis and malignancy. Given the role of **glutathione** S-transferase (GST) in detoxication, it is possible that GSTP1-1 evolved specifically to protect **proliferating** cells and share regulatory mechanisms with other cellular genes which are involved in cell division and **tumorigenesis.** We have previously shown that the expression of GSTP1 is suppressed by retinoic acid (RA) in the presence of the retinoic acid receptor (RAR) as a result of decreased

transcription from its promoter. Through deletion anal., we show here that the RA-RAR-dependent repression is mediated by the region -73 to +8. Further mutation anal. of this region indicates that the DNA sequence required for RA-RAR-dependent repression co-localizes with a consensus activator protein-1 (AP1) site essential for the promoter activity. The degree of repression correlates with the residual activity of the AP1 site. There are two adjacent G/C boxes. The one immediately downstream from the AP1 site is not essential for the promoter activity, but mutation of the second, further downstream, impairs the promoter. On the other hand, mutation of either of these two G/C boxes has little effect on RA-RAR suppression. We also show that the expression of GSTP1 is regulated by the **redox** status of the cell. Using the chloramphenicol acetyltransferase assay system, we have demonstrated that treatment with H2O2 induced transcription from the promoter and that this effect can be blocked by pre-incubation with **N-acetylcysteine** (**NAC**). It was shown that the induction by H2O2 is mediated by trans-acting factor NF-κB (nuclear factor κB), via a putative NF-κB site, 'GGGACCCTCC', located from -96 to -86. Co-transfection with an NF-κB (p65) expression construct increased the promoter activity, an effect which could be blocked by co-transfection with an IκB (MAD-3) expression construct. Deletion of the NF-κB site abolished the effect of both H2O2 and co-transfection of NF-κB. Interestingly, **NAC** is also an inducer for GSTP1. The effect of **NAC** was shown to be mediated largely by the AP1 site, since mutation of this site abolished the induction by **NAC.**

L36 ANSWER 41 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:830335 HCAPLUS
DOCUMENT NUMBER: 123:336694
TITLE: Influence of **redox** status of lymphocytes and monocytes on HIV transcription and replication
AUTHOR(S): Gougerot-Pocidalo, Marie-Anne; Aillet, Fabienne; Virelizier, Jean-Louis; Israel, Nicole
CORPORATE SOURCE: INSERM, Hopital Bichat, Paris, Fr.
SOURCE: Immunobiology (Stuttgart) (**1995**), 193(2-4), 204-9
CODEN: IMMND4; ISSN: 0171-2985
PUBLISHER: Fischer
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 27 refs. Studies with antioxidants (**NAC** or BHA) revealed that NF-κB is involved in HIV virus replication in monocyte cell lines. In vivo results suggest that one of the limitations of antioxidant therapy might be that tissue macrophages multiply the virus actively. Also, BHA or **NAC** concns. able to partially inhibit HIV replication in latently infected mononuclear cells are deleterious to the immune system, as shown by the inhibition of interleukin-2-induced **proliferation** of human mononuclear cells and of inhibition of **tumor** necrosis factor secretion by monocytic cells.

L36 ANSWER 42 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:707270 HCAPLUS
DOCUMENT NUMBER: 123:195274
TITLE: Relationship between antioxidant systems, intracellular **thiols** and DNA ploidy in liver of rats during experimental cirrhogenesis
AUTHOR(S): Sanz, Nuria; Diez-Fernandez, Carmen; Fernandez-Simon, Lourdes; Alvarez, Alberto; Cascales, Maria

CORPORATE SOURCE: Facultad Farmacia, Univ. Complutense, Madrid, 28040, Spain
SOURCE: Carcinogenesis (**1995**), 16(7), 1585-93
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hyperplastic nodular cirrhosis was induced in rats by long-term (6 mo) i.p. administration of thioacetamide at doses of 2.66 mmol/kg body weight, three times per wk. The survival rate of animals at the end of the treatment was 90%. To follow the temporal changes samples at 0, 7, 15, 30, 45, 60, 90, 150 and 180 days from rats during thioacetamide intoxication and from chronol. controls were obtained. The cirrhogenic ability of this treatment was assessed on the basis of morphol. changes: the development of macronodular cirrhosis and the appearance of fibrous septa of collagen through portal spaces. Parameters of liver injury and cholestasis were obtained by assaying the serum activities of isocitrate dehydrogenase and γ-glutamyltransferase. Enzymes and metabolites related to **glutathione redox** systems, as well as other antioxidant enzymes, were tested. Catalase and **glutathione** peroxidase, the two enzymes involved in the elimination of peroxides, and **glutathione** reductase decreased significantly at the end of the 6 mo of intoxication, while Cu-Zn and Mn superoxide dismutases increased progressively during the long-term thioacetamide treatment. Protein **thiol** levels profile showed a biphasic change increasing from the 7th day and were insensitive to the 30% depletion of intracellular **glutathione** (GSH). To study the relation of the intracellular **thiols** on the mechanisms of cell **proliferation** and differentiation during the cirrhogenic process, DNA content was assayed by flow cytometry in isolated hepatocytes, and DNA ploidy and distribution between G0-G1, S and G2 + M phases were determined Remarkable changes in relation to a sharp increase in diploid population from 7 to 180 days (24.5% → 85.5%), a pronounced decrease in polyploid populations (tetraploid + octoploid) in the same period (73.7% → 12.3%), and elevations in the populations in S phase (S1 + S2) were observed in thioacetamide-treated rats. The results obtained indicate that hepatocytes isolated from thioacetamide-treated rats showed a marked tendency to diploidy, an enhancement in DNA replication parallel to the hepatic content of protein sulfhydryl groups and a significant decline in antioxidant enzyme activities. The increase in protein **thiols** was independent of GSH level and of the **thiol redox** state.

L36 ANSWER 43 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:647796 HCAPLUS
TITLE: Increased levels of oxidized **glutathione** in CD4+ lymphocytes associated with disturbed intracellular **redox** balance in human immunodeficiency virus type 1 infection
AUTHOR(S): Aukrust, Paal; Svardal, Asbjorn M.; Mueller, Fredrik; Lunden, Bodil; Berge, Rolf K.; Ueland, Per M.; Froeland, Stig S.
CORPORATE SOURCE: Clinical Immunology Infectious Diseases, Univ. Oslo, Oslo, Norway
SOURCE: Blood (**1995**), 86(1), 258-61
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the intracellular **glutathione redox** status in isolated lymphocyte subpopulations and monocytes in patients with human immunodeficiency virus type 1 (HIV-1) infection and healthy controls. CD4+ lymphocytes from HIV-1-infected patients were primarily characterized by a substantial increase in oxidized **glutathione** levels and a considerable decrease in the ratio of reduced to total **glutathione**, in most cases below 0.5 in patients with symptomatic HIV-1 infection, rather than decreased levels of reduced **glutathione**. The increase in oxidized **glutathione** was strongly correlated with low nos. of CD4+ lymphocytes in peripheral blood and impaired stimulated interleukin-2 production and **proliferation** in peripheral blood mononuclear cells, which is compatible with an immunopathogenic role for these **redox** disturbances. The HIV-1-infected patients with the most advanced clin. and immunol. disease were also characterized by an increase in levels of reduced **glutathione** in monocytes, suggesting that the **glutathione redox** cycle may be differentially regulated in CD4+ lymphocytes and monocytes. We could not confirm previous reports suggesting cysteine deficiency as a major cause of disturbed **glutathione** homeostasis during HIV-1 infection. The demonstrated **glutathione** abnormalities were correlated with raised serum levels of **tumor** necrosis factor α. These findings suggest that a therapeutical approach, which can restore the **glutathione redox** dysbalance in CD4+ lymphocytes and decrease the inflammatory stress, may be worthwhile exploring in HIV-1 infection.

L36 ANSWER 44 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:559396 HCAPLUS
DOCUMENT NUMBER: 122:312694
TITLE: A CD4+ T cell line-secreted factor, growth promoting for normal and leukemic B cells, identified as **thioredoxin**
AUTHOR(S): Rosen, Anders; Lundman, Pia; Carlsson, Mats; Bhavani, Kasibhatla; Srinivasa, Bachally R.; Kjellstroem, Gunilla; Nilsson, Kenneth; Holmgren, Arne
CORPORATE SOURCE: Dep. Cell Biol., Univ. Linkoeping, Linkoeping, S-581 85, Swed.
SOURCE: International Immunology (**1995**), 7(4), 625-33
CODEN: INIMEN; ISSN: 0953-8178
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, a B cell growth stimulatory factor, constitutively secreted by a human CD4+ T cell hybridoma clone, MP6, has been purified and characterized. Serum-free 24 h culture media from MP6 cells were collected, concentrated by ultrafiltration and separated by gel chromatog. Fractions were analyzed for stimulatory activity using [3H]thymidine incorporation in normal and leukemic (B-CLL) B cells as target cells. Activity was present in a 12 kDa protein peak. Upon storage this lost activity indicating that the factor was sensitive to air oxidation, a well-known property of mammalian **thioredoxins** (Trxs). Treatment of the inactive fraction with **dithiothreitol** restored full activity. When culture medium was analyzed with a RIA for human placenta Trx, the MP6 clone was shown to release 30-50 ng/mL per million cells during 24 h. The B cell stimulatory activity of the MP6 medium was removed by Sepharose-bound anti-human placenta Trx IgG and activity was recovered by elution from the antibodies. Furthermore, MP6 medium showed Trx activity with NADPH and Trx reductase using an insulin disulfide reduction

assay. Starting from 5 L of serum-free MP6 conditioned medium, Trx was purified .apprx.100,000-fold. After gel electrophoresis banding, the material was analyzed by peptide sequencing and a full length sequence of an 104 amino acid long protein was obtained. This Trx sequence was identical to the previously published sequence of human Trx from HTLV-I transformed T cells, adult T cell leukemia-derived factor/Trx. A minor fraction (.apprx.30%) of the purified Trx showed alternative amino acids at eight positions; the relevance of which is discussed. MP6-derived Trx showed prominent growth stimulatory activity, measured as [3H]thymidine incorporation, and synergy was detected, particularly with IL-2, but also with IL-1β, IL-4, IL-6, **tumor** necrosis factor-α, IFN-γ, low mol. weight B cell growth factor and antiCD40 mAbs. Interestingly, the promoter for the trx gene was recently reported to contain several sequence, motifs compatible with regulated inducible transcription, especially by cytokines. Together with the authors' previous results showing a cytokine/mitogen inducible autocrine secretion of Trx from B cells, the findings point to a crucial role for extracellular Trx in **redox**-controlled mechanisms of the B lymphocyte activation cascade.

L36 ANSWER 45 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:533909 HCAPLUS
DOCUMENT NUMBER: 122:283909
TITLE: Analysis of studies related to **tumorigenicity** induced by hydroquinone
AUTHOR(S): Whysner, J.; Verna, L.; English, J. C.; Williams, G. M.
CORPORATE SOURCE: Division Pathology and Toxicology, American Health Foundation, Valhalla, NY, 10595, USA
SOURCE: Regulatory Toxicology and Pharmacology (**1995**), 21(1), 158-76
CODEN: RTOPDW; ISSN: 0273-2300
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review and discussion with many refs. which summarizes the bioassay data and analyzes information related to possible mechanisms for the **tumorigenicity** of hydroquinone (HQ). HQ produced renal adenomas in male F344 rats, and these **tumors** appeared to arise from areas of spontaneous progressive nephropathy; the nephropathy itself has been found to be enhanced by HQ. Other **neoplasms** were not confirmed to be causally related to HQ among the reported bioassays. In the male F344 rat, HQ administered alone was not DNA-reactive. HQ produced enhanced **proliferation** of renal tubular epithelium, presumably through toxicity involving **glutathione** conjugate formation. In the kidney, bone marrow, and other tissues, HQ may induce toxicity by **redox** cycling and lipid peroxidn. In bone marrow, HQ may produce microtubulin dysfunction, which is a plausible explanation for pos. cytogenetic tests, the only consistently pos. genotoxicity effect reported for HQ. Although HQ is a metabolic product of benzene, several lines of evidence suggest that the effects of HQ exposure are significantly different from those of benzene. Based upon the plausible mechanisms by which HQ may produce kidney **tumors** in male rats, the authors have concluded that occupational exposure levels of HQ are not predicted to be a **cancer** risk for humans.

L36 ANSWER 46 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:603247 HCAPLUS
DOCUMENT NUMBER: 121:203247
TITLE: Influence of **redox** status of lymphocytes and

monocytes on HIV expression and immune functions. Evaluation in vitro of antioxidant molecules as potential anti-HIV therapy
AUTHOR(S): Israel, N.; Gougerot-Pocidalo, M. A.; Aillet, F.; Virelizier, J. L.
CORPORATE SOURCE: Unite d'Immunologie Virale, Inst. Pasteur, Paris, 75724, Fr.
SOURCE: Oxid. Stress, Cell Act. Viral Infect. (**1994**) , 301-10
CODEN: 60KKAM
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The authors used BHA, a phenolic, lipid-soluble, chain-breaking antioxidant to show that peroxyl radical scavenging blocks NF-κB activation and HIV1 enhancer activity in PMA- or TNF-stimulated lymphoblastoid T (J.Jhan) and monocytic (U937) cells lines. The anti-oxidative effect of BHA was accompanied by an increase in **thiol**, but not **glutathione** , content in stimulated and unstimulated T cells, whereas TNF stimulation itself barely modified the cellular **thiol** level. Oxidative stress obtained by the addition of H2O2 to the culture medium of J.Jhan or U937 cells could not by itself induce NF-κB activation. These observations suggest that TNF and PMA do not lead to NF-κB activation through induction of changes in the cell **redox** status. Rather, TNF and PMA can exert a full activation effect only if cells are in a basal **redox** equilibrium tending towards oxidation since prior modification towards reduction by BHA treatment prevents their activation effects. The effects of BHA or **NAC**, a known **glutathione** precursor, were investigated also on the regulation of HIV1 expression in latently infected U1 cells and in the productively and chronically infected U937 cells. Both antioxidants inhibited TNF- or PMA-induced NF-κB activity in U1 cells in parallel with a partial decrease in induction of HIV replication. Both prevented the sustained NF-κB activity permanently induced by the virus in HIV chronically infected U937 but intriguingly did not modify HIV replication. This may be a limitation to potential antiviral effects of antioxidant therapies. Another limitation may be that antiviral (at least partially) concns. of **NAC** or BHA inhibited IL2-induced human PBMC **proliferation** and also secretion of TNF in PMA-stimulated U937 cells.

L36 ANSWER 47 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:602520 HCAPLUS
DOCUMENT NUMBER: 121:202520
TITLE: Abnormal **redox** regulation in HIV infection and other immunodeficiency diseases
AUTHOR(S): Droge, W.; Eck, H. P.; Mihm, S.; Galter, D.
CORPORATE SOURCE: Div. Immunochem., Deutsches Krebsforschungszentrum, Heidelberg, D-6900, Germany
SOURCE: Oxid. Stress, Cell Act. Viral Infect. (**1994**) , 285-99
CODEN: 60KKAM
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 66 refs. HIV-infected persons at all stages of the disease have on the average markedly decreased plasma cystine and cysteine concns., decreased intracellular **glutathione** and elevated plasma glutamate levels. Elevated extracellular glutamate levels aggravate the cysteine deficiency since glutamate inhibits competitively the membrane transport of cystine. Lymphocyte functions in vitro are augmented even by moderate elevations of extracellular cysteine and inhibited by elevation

of the extracellular glutamate concns. A significant correlation between individual CD4+ T cell nos. and individual cystine and glutamate levels has also been found in a cohort of HIV-infected persons, in healthy human blood donors, and in chimpanzees. CD8+ T cells showed no significant correlation. A rapid and significant decrease of plasma cysteine levels and increase of plasma glutamate was also found in rhesus macaques 2 wk after infection with the closely related SIVmac, but not in HIV-infected chimpanzees or SIVagm-infected African green monkeys. (The latter two species do not develop AIDS-like symptoms.). Elevated plasma glutamate levels were found to be neg. correlated with lymphocyte functions also in **cancer** patients. In view of the decreased levels of the bona fide antioxidants cysteine and **glutathione** one may expect to find manifestations of oxidative damage. Indeed, elevated levels of malondialdehyde have been demonstrated, but the contribution of oxidative damage to the immunopathol. of HIV infection remains to be determined A cysteine deficiency is also expected to compromise certain **glutathione**-dependent immunol. functions, such as IL-2 dependent **proliferation** and activation of cytotoxic T cells. The activation of the transcription factor NFκB which controls the inducible transcription of several immunol. relevant genes, in contrast, was found to be neg. correlated with the extracellular cysteine supply. This indicates that the overactivation of several immunol. functions in the early stages of the disease, including the overexpression of an interleukin-2 receptor α-chain cleavage product, TNFα and β2-microglobulin may also be the consequence of the HIV-induced cysteine deficiency. The replication of HIV-1, i.e. another gene under control of NFκB binding sites, was shown to be inhibited by cysteine or N-acetyl-cysteine (**NAC**). In view of the established cysteine and **glutathione** deficiency in HIV-infected persons, the authors have proposed to consider N-acetyl-cysteine for the treatment of these patients. **NAC** is a well established and safe drug with well documented toxicol. and pharmacokinetics.

L36 ANSWER 48 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:577403 HCAPLUS
DOCUMENT NUMBER: 121:177403
TITLE: Antioxidant and staurosporine inhibit stimulation of the transcription regulator NF-κB following **tumor** necrosis factor treatment of chronic B-leukemia cells
AUTHOR(S): Jabbar, Shireen A. B.; Hoffbrand, A. Victor; Wickremasinghe, R. Gitendra
CORPORATE SOURCE: Department of Haematology, Royal Free Hospital School of Medicine, London, NW3 2QG, UK
SOURCE: Leukemia Research (**1994**), 18(7), 523-30
CODEN: LEREDD; ISSN: 0145-2126
DOCUMENT TYPE: Journal
LANGUAGE: English
AB B-chronic lymphocytic leukemia (B-CLL) and hairy cell leukemia cells (HCL) are refractory to stimulation by several cytokines which activate normal B-cells. However, **tumor** necrosis factor (TNF) promotes the **proliferation** of these cells. TNF regulates some of its cellular responses via the transcription factor NF-κB. Using an electrophoretic mobility shift assay, we demonstrate that TNF treatment of B-CLL and HCL cells in vitro resulted in the augmentation of NF-κB levels. In hemopoietic cell lines, TNF induction of NF-κB is mediated via the generation of reactive oxygen intermediates and by the activation of protein kinase C (PKC). We have used activators and inhibitors of these pathways to unravel TNF signalling in the cells of ten

patients with B-CLL and two with HCL, using the increase in NF-κB levels following TNF treatment as an end point. Raising **glutathione** levels with N-acetyl cysteine substantially reduced NF-κB induction by TNF in two of four samples, as did treatment of cells with the antioxidant butylated-hydroxytoluene in all three samples tested. These data suggest that **redox** mechanisms are involved in TNF signalling in these cells. Treatment with the PKC activator phorbol myristate acetate failed to activate NF-κB suggesting that this enzyme does not mediate the induction of NF-κB in these cells. However, the protein kinase inhibitor staurosporine inhibited TNF induction of NF-κB in four of five samples, suggesting that staurosporine-sensitive protein kinases (other than PKC) are involved in the signalling pathway. Our results suggest that PKC-independent pathways, including pathways sensitive to **redox** reagents, mediate the induction of NF-κB by TNF in chronic B-leukemia cells. Addnl., these data suggest that defects in PKC-mediated pathways may contribute to the general reluctance of B-CLL and HCL cells to respond to mitogenic signals.

L36 ANSWER 49 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:505379 HCAPLUS
DOCUMENT NUMBER: 121:105379
TITLE: Oxidative damage and repair in the developing nervous system
AUTHOR(S): Verity, M. Anthony
CORPORATE SOURCE: Division Neuropathology and Brain Research Institute, UCLA Center the Health Sciences, Los Angeles, CA, 90024-1732, USA
SOURCE: Neurotoxicology (**1994**), 15(1), 81-91
CODEN: NRTXDN; ISSN: 0161-813X
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 88 refs. Excessive production of reactive oxygen species (ROS) is a recognized cause of cell injury. In contrast to such well recognized cell injury, oxidative stress plays a role in cell **proliferation**, differentiation and **tumor** promotion. This review examines the role of oxidative stress in initiating and promoting the establishment of normal or abnormal neuronal patterns and subsequent neurogenesis within the central and peripheral nervous system. In particular, the role of apoptosis in both normal and abnormal neuronal development and maturation will be examined with special reference to the induction of apoptotic cell death following abusive ligand-induced ion movements. The interaction of oxidant stress and immediate-early response gene activation is discussed with further reference to the induction of apoptosis. While glutamate receptor activation appears mandatory for coordinate maturation and neuritogenesis, such neuronal survival and differentiation is intimately dependent upon the intracellular **glutathione redox** potential, maintained by cystine uptake. Selected examples of reactive oxygen species induced injury pertaining to developmental neurotoxicol. are presented and include starvation, irradiation injury and glutamate excitotoxicity.

L36 ANSWER 50 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:429020 HCAPLUS
DOCUMENT NUMBER: 121:29020
TITLE: Pathobiological effects of acetaldehyde in cultured human epithelial cells and fibroblasts
AUTHOR(S): Grafstroem, Roland C.; Dypbukt, Jeannette, M.;

Sundqvist, Kristina; Atzori, Luigi; Nielsen, Inge; Curren, Rodger D.; Harris, Curtis C.
CORPORATE SOURCE: Inst. Environ. Med., Karolinska Inst., Stockholm, S-171 77, Swed.
SOURCE: Carcinogenesis (**1994**), 15(5), 985-90
CODEN: CRNGDP; ISSN: 0143-3334
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ability of acetaldehyde, a respiratory **carcinogen** present in tobacco smoke and automotive emissions, to affect cell viability, **thiol** status and intracellular Ca2+ levels and to cause DNA damage and mutations has been studied using cultured human cells. Within a concentration range of 3-100 mM, a 1 h exposure to acetaldehyde decreases colony survival and inhibits uptake of the vital dye neutral red in bronchial epithelial cells. Acetaldehyde also causes both DNA interstrand cross-links and DNA protein cross-links whereas no DNA single strand breaks are detected. The cellular content of **glutathione** is also decreased by acetaldehyde, albeit, without concomitant changes in the **glutathione redox** status or in the content of protein **thiols.** Transient or sustained increases in cytosolic Ca2+ occur within minutes following exposure of cells to acetaldehyde. Moreover, acetaldehyde significantly decreases the activity of the DNA repair enzyme O6-methylguanine-DNA methyltransferase. Finally, a 5 h exposure to acetaldehyde causes significant levels of 6-thioguanine resistance mutations in an established mutagenesis model involving skin fibroblasts. The results indicate that mM concns. of acetaldehyde cause a wide range of cytopathic effects associated with multistep **carcinogenesis.** The fact that acetaldehyde, in relation to its cytotoxicity, causes comparatively higher genotoxicity and inhibits DNA repair more readily than other major aldehydes in tobacco smoke and automotive emissions is discussed.

L36 ANSWER 51 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:515121 HCAPLUS
DOCUMENT NUMBER: 119:115121
TITLE: Augmentation of cytostatic effect of recombinant human lymphotoxin and involvement of **glutathione redox** cycle
AUTHOR(S): Matsunaga, K.; Mashiba, H.
CORPORATE SOURCE: Div. Immunol., Natl. Kyushu Cancer Cent., Fukuoka, 812, Japan
SOURCE: European Cytokine Network (**1992**), 3(3), 307-11
CODEN: ECYNEJ; ISSN: 1148-5493
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of **buthionine sulfoximine** (BSO), an inhibitor of **glutathione** biosynthesis, in combined use with a nitrosourea derivative, ACNU, on the cytostatic effect of recombinant human lymphotoxin (rhLT) was studied in vitro. The simultaneous addition of 0.02 mM or 0.5 mM BSO and rhLT slightly augmented the inhibition of Meth A **tumor** cell **proliferation.** A similar tendency was observed when the target cells were treated with 0.02 mM or 0.5 mM BSO for 24 h prior to the addition of rhLT. A marked augmentation of the **antiproliferative** effect was obtained when the target cells were treated in vitro with 0.005 mM or 0.02 mM BSO prior to the addition of 0.02 mM or 0.1 mM BSO and rhLT. The addition of ACNU simultaneously with rhLT to BSO-treated cells also augmented the **antiproliferative** effect.

These results suggest that the **glutathione redox** cycle is closely related to the mechanism of LT-induced cytotoxicity.

L36 ANSWER 52 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:39448 HCAPLUS
DOCUMENT NUMBER: 116:39448
TITLE: Red cell regulation of **tumor** necrosis factor-induced human neutrophil cytostatic activity
AUTHOR(S): Shau, Hungyi
CORPORATE SOURCE: Sch. Med., UCLA, Los Angeles, CA, 90024-1782, USA
SOURCE: Cancer Communications (**1991**), 3(9), 283-6
CODEN: CNCMET; ISSN: 0955-3541
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Tumor** necrosis factor (TNF) activates polymorphonuclear neutrophils (PMN) to suppress **tumor** cell **proliferation**. This cytostatic activity could be blocked by the addition of red blood cells (RBC) into the assay. TNF-induced PMN cytostatic activity was mediated by hydrogen peroxide. RBC have two major pathways to detoxify H2O2, one by catalase and the other by the **glutathione redox** cycle. Therefore, the catalase inhibitor 3-amino-1,2,4-triazole (AT) and the **glutathione** inhibitor N-ethylmaleimide (NE) were used to assess the role of each anti-oxidant in protecting the **tumor** target cells. RBC, depleted of catalase by AT, no longer protected Raji **tumor** cells from PMN cytostatic activity. However, depletion of reduced **glutathione** by NE had no effect on RBC protection of **tumor** target cells. Thus, RBC can protect **tumor** cells from cytostatic activity mediated by TNF-activated PMN, and the protection is a function of catalase, but not **glutathione.**

L36 ANSWER 53 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:441503 HCAPLUS
DOCUMENT NUMBER: 115:41503
TITLE: Augmented **antiproliferative** effect in combined use of human lymphotoxin with a nitrosourea derivative, ACNU, and the involvement of **glutathione redox** cycle
AUTHOR(S): Mashiba, Harukazu; Matsunaga, Keiko; Kakutani, Tetsu
CORPORATE SOURCE: Div. Immunol., Natl. Kyushu Cancer Cent., Fukuoka, 815, Japan
SOURCE: International Journal of Immunopharmacology ( **1991**), 13(4), 333-8
CODEN: IJIMDS; ISSN: 0192-0561
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cytotoxic or cytostatic effect of the combined use of human lymphotoxin (LT) with 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea-HCl (ACNU) on L cells or Meth A **tumor** cells was studied. Simultaneous addition of LT derived from a human lymphoid cell line with ACNU (200 or 500 μg/mL) significantly augmented the cytotoxic effect. Similar augmented inhibition was obtained when LT was added to ACNU-treated L cells. The pretreatment of Meth A **tumor** cells with ACNU (25 or 50 μg/mL) augmented recombinant human LT-mediated cytostasis. However, the addition of **glutathione** (1.0 mg/mL) to ACNU-treated Meth A **tumor** cells significantly nullified the augmented **antiproliferative** effect of LT (10 U/mL). These results suggest that augmentation of the **antiproliferative** effect on **tumor** cells could be induced

through the combined use of LT with ACNU by lowering the intracellular level of **glutathione.**

L36 ANSWER 54 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:400358 HCAPLUS
DOCUMENT NUMBER: 109:358
TITLE: Toxic effects of acute **glutathione** depletion by **buthionine sulfoximine** and dimethylfumarate on murine mammary **carcinoma** cells
AUTHOR(S): Dethlefsen, L. A.; Lehman, C. M.; Biaglow, J. E.; Peck, V. M.
CORPORATE SOURCE: Health Sci. Cent., Univ. Utah Health, Salt Lake City, UT, 84132, USA
SOURCE: Radiation Research (**1988**), 114(2), 215-24
CODEN: RAREAE; ISSN: 0033-7587
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Glutathione** depletion to .simeq.5% of control for 48 h or longer by 0.05 mM L-**buthionine sulfoximine** (BSO) led to appreciable toxicity for the 66 murine mammary **carcinoma** cells growing in vitro [L. A. Dethlefsen et al., 1986]. Such toxicity in normal, **proliferating** cells in vivo would be undesirable. Thus the toxic effects after acute GSH depletion to .simeq.5% of control by BSO plus dimethylfumarate (DMF) were evaluated in these same 66 cells to determine if this anti-**proliferative** effect could be minimized. Two hours of 0.025 mM DMF reduced GSH to 45% of control, while 6 h of 0.05 mM BSO reduced it to 16%. However, BSO (6 h) plus DMF (2 h) and BSO (24 h) plus DMF (2 h) reduced GSH to 4 and 2%, resp. The incorporation (15-min pulses) of radioactive precursors into protein and RNA were unaffected by these treatment protocols. In contrast, cell growth was only modestly affected, but the incorporation of [3H]thymidine into DNA was reduced to 64% of control by the BSO (24 h) plus DMF (2 h) protocol even though it was unaffected by the BSO (6 h) plus DMF (2 h) treatment. However, the aerobic radiation response, as measured by cell survival, was not modified at doses of either 4.0 or 8.0 Gy. The growth rates of treated cultures, after drug removal, quickly returned to control rates and the resynthesis of GSH in cells from both protocols was also rapid. The GSH levels after either protocol were slightly above control by 12 h after drug removal, dramatically over control (.simeq.200%) by 24 h, and back to normal by 48 h. Thus even a relatively short treatment with BSO and DMF resulting in a GSH depletion to 2-5% of control had a marked effect on DNA synthesis and plating efficiency and a modest effect on cellular growth. Presumably the **antiproliferative** effects are due to a depletion of nuclear GSH with the subsequent inhibition of the GSH/**glutaredoxin**-mediated conversion of ribonucleotides to deoxyribonucleotides. However, even after extended treatment, upon drug removal, GSH was rapidly resynthesized and cellular DNA synthesis and growth quickly resumed.

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=> d que stat l38
L1             1 SEA FILE=REGISTRY ABB=ON  ETHACRYNIC ACID/CN
L2             1 SEA FILE=REGISTRY ABB=ON  PDTC/CN
L4             1 SEA FILE=REGISTRY ABB=ON  2,3-DIMERCAPTO-1-PROPANESULFONIC
                 ACID/CN
L5             1 SEA FILE=REGISTRY ABB=ON  DITHIOCARBAMATE/CN
L6             1 SEA FILE=REGISTRY ABB=ON  DITHIOTHREITOL/CN
L8             1 SEA FILE=REGISTRY ABB=ON  BUTHIONINE SULFOXIMINE/CN
L9             1 SEA FILE=REGISTRY ABB=ON  METHIONINE SULFOXIMINE/CN
L11            1 SEA FILE=REGISTRY ABB=ON  N-ACETYLCYSTEINE/CN
L12            1 SEA FILE=REGISTRY ABB=ON  CYSTEAMINE/CN
L13            2 SEA FILE=REGISTRY ABB=ON  LIPOIC ACID/CN
L14            1 SEA FILE=REGISTRY ABB=ON  THIOCTIC ACID/CN
L16            3 SEA FILE=REGISTRY ABB=ON  DMSA/CN
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L19            1 SEA FILE=REGISTRY ABB=ON  DITHIOTHREITOL/CN
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L24           17 SEA FILE=REGISTRY ABB=ON  L1 OR L2 OR L4 OR L5 OR L6 OR L8 OR
                 L9 OR L11 OR L12 OR L13 OR L14 OR L16 OR L17 OR L18 OR L19 OR
                 L21 OR L23
L25        23859 SEA FILE=HCAPLUS ABB=ON  L24
L26       146867 SEA FILE=HCAPLUS ABB=ON  L25 OR (?ETHACRYNIC? OR (2,3-DIMERCAPT
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                 EINE? OR NAC OR ?CYSTEAMINE?)
L27       149253 SEA FILE=HCAPLUS ABB=ON  L26 OR (?LIPOIC? OR ?THIOCTIC? OR
                 2-MERCAPTO-1-PROPANESULFONIC?)(W)?ACID? OR DMSA OR MESNA OR
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L28         7586 SEA FILE=HCAPLUS ABB=ON  L27 AND ?REDOX?
L29         1110 SEA FILE=HCAPLUS ABB=ON  L28 AND (?CANCER? OR ?CARCIN? OR
                 ?NEOPLAS? OR ?TUMOR? OR ?TUMOUR?)
L30          199 SEA FILE=HCAPLUS ABB=ON  L29 AND ?PROLIFERAT?
L31           48 SEA FILE=HCAPLUS ABB=ON  L30 AND ?THIOL?
L34           54 SEA FILE=HCAPLUS ABB=ON  L30 AND (PRD<19990216 OR PD<19990216)
L35           85 SEA FILE=HCAPLUS ABB=ON  L31 OR L34
L37          103 SEA L35
L38           67 DUP REMOV L37 (36 DUPLICATES REMOVED)

=> d ibib abs l38 1-67

L38  ANSWER 1 OF 67     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:   2005266362     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 15792952
TITLE:              Mechanistic studies on a novel, highly potent
                    gold-phosphole inhibitor of human glutathione
                    reductase.
AUTHOR:             Deponte Marcel; Urig Sabine; Arscott L David; Fritz-Wolf
                    Karin; Reau Regis; Herold-Mende Christel; Koncarevic Sasa;
                    Meyer Markus; Davioud-Charvet Elisabeth; Ballou David P;
                    Williams Charles H Jr; Becker Katja
CORPORATE SOURCE:   Interdisciplinary Research Center, Justus Liebig
                    University, D-35392 Giessen, Germany.
CONTRACT NUMBER:    GM11106 (NIGMS)
SOURCE:             Journal of biological chemistry, (2005 May 27) 280 (21)
                    20628-37.  Electronic Publication: 2005-03-24.
                    Journal code: 2985121R. ISSN: 0021-9258.
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PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200508
ENTRY DATE: Entered STN: 20050524
Last Updated on STN: 20050816
Entered Medline: 20050815

AB The homodimeric flavoprotein **glutathione** reductase (GR) is a central player of cellular **redox** metabolism, connecting NADPH to the large pool of **redox**-active **thiols.** In this work, the inhibition of human GR by a novel gold-phosphole inhibitor (GoPI) has been studied in vitro. Two modes of inhibition are observed, reversible inhibition that is competitive with GSSG followed by irreversible inhibition. When approximately 1 nm GoPI is incubated with NADPH-reduced GR (1.4 nm) the enzyme becomes 50% inhibited. This appears to be the most potent stable inhibitor of human GR to date. Analyzing the monophasic oxidative half-reaction of reduced GR with GSSG at pH 6.9 revealed a K(d)((app)) for GSSG of 63 microm, and a k((obs)max) of 106 s(-1) at 4 degrees C. The reversible inhibition by the gold-phosphole complex [{1-phenyl-2,5-di(2-pyridyl)phosphole}AuCl] involves formation of a complex at the GSSG-binding site of GR (K(d) = 0.46 microm) followed by nucleophilic attack of an active site cysteine residue that leads to covalent modification and complete inactivation of the enzyme. Data from titration spectra, molecular modeling, stopped-flow, and steady-state kinetics support this theory. In addition, covalent binding of the inhibitor to human GR was demonstrated by mass spectrometry. The extraordinary properties of the compound and its derivatives might be exploited for cell biological studies or medical applications, e.g. as an anti-**tumor** or antiparasitic drug. Preliminary experiments with glioblastoma cells cultured in vitro indicate an anti-**proliferative** effect of the inhibitor in the lower micromolar range.

L38 ANSWER 2 OF 67 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2005250952 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15890017
TITLE: Differential susceptibility of nonmalignant human breast epithelial cells and breast **cancer** cells to **thiol** antioxidant-induced G(1)-delay.
AUTHOR: Menon Sarita G; Coleman Mitchell C; Walsh Susan A; Spitz Douglas R; Goswami Prabhat C
CORPORATE SOURCE: Free Radical and Radiation Biology Program, Department of Radiation Oncology, University of Iowa, Iowa City, IA 52242, USA.
CONTRACT NUMBER: CA66081 (NCI)
HL51469 (NHLBI)
SOURCE: Antioxidants & redox signalling, (2005 May-Jun) 7 (5-6) 711-8.
Journal code: 100888899. ISSN: 1523-0864.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20050514
Last Updated on STN: 20050607

AB Reactive oxygen species (ROS) and ROS signaling have been implicated in a variety of human pathophysiological conditions that involve aberrant cellular **proliferation**, particularly **cancer.** We

hypothesize that intracellular **redox** state differentially affects cell-cycle progression in nonmalignant versus malignant cells. The **thiol** antioxidant, N-acetyl-L-cysteine (**NAC**), was used to alter intracellular **redox** state in nonmalignant human breast epithelial (MCF-10A) and breast **cancer** cells (MCF-7 and MDA-MB-231). Treatment of cells with **NAC** resulted in significant augmentation of intracellular small-molecular-weight **thiols**, **glutathione** and cysteine. In addition, **NAC** treatment decreased oxidation of a prooxidant-sensitive dye in MCF-10A cells, but not in MDA-MB-231 and MCF-7 cells. **NAC** -induced shifts in intracellular **redox** state toward a more reducing environment caused G(1) delays in MCF-10A cells without causing any significant changes in MCF-7 and MDA-MB-231 cell-cycle progression. **NAC** treatment of MCF-10A (but not MCF-7 and MDA-MB-231) was accompanied by a decrease in cyclin D1 and an increase in p27 protein levels, which correlated with increased retinoblastoma protein hypophosphorylation. These results show differential **redox** control of progression from G(1) to S in nonmalignant versus malignant cells and support the hypothesis that loss of a **redox** control of the cell cycle could contribute to aberrant **proliferation** seen in **cancer** cells.

L38 ANSWER 3 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2005382451 EMBASE
TITLE: Proceedings from the "Third International Conference on Mechanism of Action of Nutraceuticals".
AUTHOR: Mandel S.; Packer L.; Youdim M.B.H.; Weinreb O.
CORPORATE SOURCE: O. Weinreb, Department of Pharmacology, Technion-Faculty of Medicine, P.O.B. 9697, Haifa 31096, Israel. worly@tx.technion.ac.il
SOURCE: Journal of Nutritional Biochemistry, (2005) Vol. 16, No. 9, pp. 513-520.
Refs: 56
ISSN: 0955-2863 CODEN: JNBIEL
PUBLISHER IDENT.: S 0955-2863(05)00059-8
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050915
Last Updated on STN: 20050915

AB The "Third International Conference on Mechanisms of Action of Nutraceuticals" (ICMAN 3) was held to bring investigators from around the world together to find answers and share experience relevant to the role of nutraceuticals in health and disease. Dietary supplements are currently receiving recognition as being beneficial in coronary heart disease, **cancer**, osteoporosis and other chronic and degenerative diseases such as diabetes, Parkinson's and Alzheimer's diseases. This gave impetus to investigate the mechanisms of action of nutraceuticals and related bioactive compounds in disease pathologies. Many lines of evidence indicate that the mechanistic actions of natural compounds involve a wide array of biological processes, including activation of antioxidant defenses, signal transduction pathways, cell survival-associated gene expression, cell **proliferation** and differentiation and preservation of mitochondrial integrity. Furthermore,

many of these compounds exert anti-inflammatory actions through inhibition of oxidative stress-induced transcription factors (e.g., NF-κB, AP-1), cytotoxic cytokines and cyclooxygenase-2. It appears that these properties play a crucial role in the protection against the pathologies of numerous age-related or chronic diseases. This review summarizes the latest research finding in functional foods and micronutrients in the promotion of health and reduction of risk for major chronic diseases as presented in this symposium. 

L38 ANSWER 4 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2005312756 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15746213
TITLE: Extracellular cysteine/cystine **redox** regulates the p44/p42 MAPK pathway by metalloproteinase-dependent epidermal growth factor receptor signaling.
AUTHOR: Nkabyo Yvonne S; Go Young-Mi; Ziegler Thomas R; Jones Dean P
CORPORATE SOURCE: Graduate Program in Molecular and Systems Pharmacology, Emory University, Atlanta, Georgia 30322, USA.
CONTRACT NUMBER: DK-55850 (NIDDK)
ES-011195 (NIEHS)
SOURCE: American journal of physiology. Gastrointestinal and liver physiology, (2005 Jul) 289 (1) G70-8. Electronic Publication: 2005-03-03.
Journal code: 100901227. ISSN: 0193-1857.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200508
ENTRY DATE: Entered STN: 20050618
Last Updated on STN: 20050803
Entered Medline: 20050802

AB Previous research shows that stimulation of **proliferation** of colon **carcinoma** (Caco-2) cells by a more reduced extracellular cysteine/cystine (Cys/CySS) **redox** state occurs with no apparent effect on intracellular **glutathione** and that this stimulation is lost on addition of epidermal growth factor. The purpose of the present study was to determine whether a more reduced extracellular Cys/CySS **redox** state activates the mitogenic p44/p42 mitogen-activated protein kinase (MAPK) pathway and whether this is signaled through the epidermal growth factor receptor (EGFR). Caco-2 cells were exposed to a range of physiological extracellular **redox** conditions from -150 to 0 mV. In the absence of added growth factors, the most reduced (-150 mV) **redox** state induced an 80% increase in EGFR phosphorylation, and this was followed by a marked increase in phosphorylation of p44/p42 MAPK. Inhibitors of EGFR (AG1478) and p44/p42 MAPK (U0126) phosphorylation blocked **redox**-dependent p44/p42 phosphorylation, indicating that signaling occurred by EGFR. These effects were inhibited by pretreatment with a nonpermeant alkylating agent, showing that signaling involved **thiols** accessible to the extracellular space. The EGFR ligand TGF-alpha was increased in culture medium at more reduced **redox** states. **Redox**-dependent phosphorylation of EGFR was completely prevented by a metalloproteinase inhibitor (GM6001), and an antibody to TGF-alpha partially inhibited the phosphorylation of p44/p42 MAPK by **redox.** Thus the data show that a **redox** -dependent activation of metalloproteinase can stimulate the mitogenic p44/p42 MAPK pathway by a TGF-alpha-dependent mechanism. Because Cys

availability and Cys/CySS **redox** are dependent on nutrition, disease, and environmental exposures, the results suggest that cell **proliferation** could be influenced physiologically by Cys-dependent **redox** effects on growth factor signaling pathways.

L38 ANSWER 5 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2005222593 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15684606
TITLE: The **thioredoxin** reductase/**thioredoxin** system: novel **redox** targets for **cancer** therapy.
AUTHOR: Biaglow John E; Miller Richard A
CORPORATE SOURCE: Department of Radiation Oncology and Biochemistry, University of Pennsylvania Medical School, Philadelphia 19104, USA.. Biaglow@xrt.upenn.edu
SOURCE: Cancer biology & therapy, (2005 Jan) 4 (1) 6-13. Electronic Publication: 2004-01-08. Ref: 79 Journal code: 101137842. ISSN: 1538-4047.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 20050429 Last Updated on STN: 20050916 Entered Medline: 20050915

AB **Thioredoxin** reductase (TRX) is a selenoprotein that reduces oxidized protein substrates in an NADPH-dependent process (cf. Fig. 1). The **thioredoxins** (TX) are a family of small **redox** active proteins that undergo reversible oxidation/reduction and help to maintain the **redox** state of cells. TX serves as a cofactor in many TRX-catalyzed reductions in a manner similar to **glutathione** (GSH) in **thioltransferase** reactions. For example, TX is a cofactor in protein disulfide reduction and DNA synthesis, but independently, it inhibits apoptosis, stimulates cell **proliferation** and angiogenesis, and increases transcription factor activity. The role of the TRX/TX system is limited by its reducing capacity as well as the additional supply of electrons in the form of NADPH provided by hexose monophosphate shunt (HMPS). TX is limited by the reduction capacity of its vicinal sulfhydryls and needs a source of electrons from the HMPS and TRX- coupled system to reduce disulfides. Oxidized TX is reduced by TRX and NADPH. Several lines of evidence suggest that the coupled HMPS/TRX/TX system represents an important target for **cancer** therapy. TX overexpression has been reported in several malignancies and may be associated with aggressive **tumor** growth and poor survival. In some cells, TX is an important factor in conferring resistance to chemotherapy and in stimulating production of hypoxia-inducible factor (HIF-1). Several inhibitors of the TRX/TX system have been evaluated in experimental **cancer** models: these include HMPS inhibitors, carbohydrate analogues, NADP synthesis blockers, vicinal **thiol** reactants, cisplatin, and TRX inhibitors. More recently, the targeted anti-**cancer** agent motexafin gadolinium has been identified. Motexafin gadolinium is a **redox** mediator that selectively localizes to **cancer** cells, and reacts with reducing metabolites and vicinal **thiols** to generate reactive oxygen species that ultimately block the TRX enzyme as well as the analogous **glutaredoxin** activity. In cell and animal models, motexafin gadolinium is directly cytotoxic to various **tumor** cells and

enhances the activity of radiation therapy and chemotherapy. This drug is now in a broad range of clinical trials investigating its therapeutic potential when used as a single agent or in combination with either chemotherapy or radiation therapy. Promising clinical activity has been reported in a clinical trial with motexafin gadolinium and whole brain radiation therapy for treatment of brain metastases from solid **tumors.** These findings suggest that the TRX/TX system may represent an attractive target for development of new **cancer** therapeutics.

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ACCESSION NUMBER: 2005306014 EMBASE
TITLE: Extracellular cysteine/cystine **redox** regulates the p44/p42 MAPK pathway by metalloproteinase-dependent epidermal growth factor receptor signaling.
AUTHOR: Nkabyo Y.S.; Go Y.-M.; Ziegler T.R.; Jones D.P.
CORPORATE SOURCE: D.P. Jones, Dept. of Medicine, Whitehead Biomedical Research Center, Emory Univ., 615 Michael St., Atlanta, GA 30322, United States. dpjones@emory.edu
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (2005) Vol. 289, No. 1 52-1, pp. G70-G78.
Refs: 42
ISSN: 0193-1857 CODEN: APGPDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050721
Last Updated on STN: 20050721

AB Previous research shows that stimulation of **proliferation** of colon **carcinoma** (Caco-2) cells by a more reduced extracellular cysteine/cystine (Cys/CySS) **redox** state occurs with no apparent effect on intracellular **glutathione** and that this stimulation is lost on addition of epidermal growth factor. The purpose of the present study was to determine whether a more reduced extracellular Cys/CySS **redox** state activates the mitogenic p44/p42 mitogen-activated protein kinase (MAPK) pathway and whether this is signaled through the epidermal growth factor receptor (EGFR). Caco-2 cells were exposed to a range of physiological extracellular **redox** conditions from -150 to 0 mV. In the absence of added growth factors, the most reduced (-150 mV) **redox** state induced an 80% increase in EGFR phosphorylation, and this was followed by a marked increase in phosphorylation of p44/p42 MAPK. Inhibitors of EGFR (AG1478) and p44/p42 MAPK (U0126) phosphorylation blocked **redox**-dependent p44/p42 phosphorylation, indicating that signaling occurred by EGFR. These effects were inhibited by pretreatment with a nonpermeant alkylating agent, showing that signaling involved **thiols** accessible to the extracellular space. The EGFR ligand TGF-α was increased in culture medium at more reduced **redox** states. **Redox**-dependent phosphorylation of EGFR was completely prevented by a metalloproteinase inhibitor (GM6001), and an antibody to TGF-α partially inhibited the phosphorylation of p44/p42 MAPK by **redox.** Thus the data show that a **redox**-dependent activation of metalloproteinase can stimulate the mitogenic p44/p42 MAPK pathway by a TGF-α-dependent mechanism. Because Cys availability and Cys/CySS **redox** are

dependent on nutrition, disease, and environmental exposures, the results suggest that cell **proliferation** could be influenced physiologically by Cys-dependent **redox** effects on growth factor signaling pathways. Copyright .COPYRGT. 2005 the American Physiological Society.

L38 ANSWER 7 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2004109223 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14998722
TITLE: **Thiol** antioxidant and **thiol**-reducing agents attenuate 15-deoxy-delta 12,14-prostaglandin J2-induced heme oxygenase-1 expression.
AUTHOR: Liu Jean-Dean; Tsai Shu-Huei; Lin Shyr-Yi; Ho Yuan-Soon; Hung Ling-Fang; Pan Shiann; Ho Feng-Ming; Lin Chun-Mao; Liang Yu-Chih
CORPORATE SOURCE: College of Medicine, Taipei Medical University, Taipei, Taiwan.. ycliang@tmu.edu.tw
SOURCE: Life sciences, (2004 Mar 26) 74 (19) 2451-63. Journal code: 0375521. ISSN: 0024-3205.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040305
Last Updated on STN: 20040403
Entered Medline: 20040402

AB Heme oxygenase-1 (HO-1) is induced as a beneficial and adaptive response in cells and tissues exposed to oxidative stress. Herein we examined how various eicosanoids affect the induction of HO-1, and the possible mechanism underlying 15-deoxy-Delta(12,14)- prostaglandin J(2) (15d-PGJ(2))-induced HO-1 expression. PGH(2), PGD(2) and its metabolites of the PGJ(2) series, and PGA(1) markedly induced the protein expression of HO-1. Arachidonic acid (AA), docosahexaenoic acid (DHA), PGE(2), PGF(2 alpha), and thromboxane B(2) (TXB(2)) were shown to have no effect on the induction of HO-1. 15d-PGJ(2) was the most potent activator achieving significance at 5 microM. Although 15d-PGJ(2) significantly activated the MAPKs of JNK and ERK, the activation of JNK and ERK did not contribute to the induction of HO-1 as determined using transfection of dominant-negative plasmids and MAPKs inhibitors. Additional experiment indicated that 15d-PGJ(2) induced HO-1 expression through peroxisome **proliferator**-activated receptor (PPAR)-independent pathway. 15d-PGJ(2) significantly decreased the intracellular level of reduced **glutathione**; and the **thiol** antioxidant, N-acetyl-L-cysteine (**NAC**), and the **thiol**-reducing agent, **dithiothreitol** (DTT), inhibited the induction of HO-1 by 15d-PGJ(2). Finally, **NAC** and DTT exhibited significant inhibition of HO-1 mRNA and HO-1 promoter reporter activity induced by 15d-PGJ(2). These results suggest that **thiol** antioxidant and reducing agents attenuate the expression of HO-1 induced by 15d-PGJ(2), and that the cellular **thiol**-disulfide **redox** status may be linked to HO-1 activation.

L38 ANSWER 8 OF 67 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2005028939 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15480664
TITLE: Sodium selenite induces apoptosis in acute promyelocytic leukemia-derived NB4 cells by a caspase-3-dependent mechanism and a **redox** pathway different from that

of arsenic trioxide.
AUTHOR: Zuo Lu; Li Jian; Yang Yang; Wang Xuan; Shen Ti; Xu Cai-min; Zhang Zhi-nan
CORPORATE SOURCE: Department of Hematology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, 100730, Beijing, People's Republic of China.
SOURCE: Annals of hematology, (2004 Dec) 83 (12) 751-8. Electronic Publication: 2004-10-06.
Journal code: 9107334. ISSN: 0939-5555.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 20050120
Last Updated on STN: 20050318
Entered Medline: 20050317

AB Two relatively recent discoveries stand behind our current effort to investigate the effects of the chemopreventive agent, selenium, on the **proliferation** and survival of NB4 cells. The first is that certain selenium compounds such as sodium selenite have pro-oxidant ability to catalyze the oxidation of **thiols** and simultaneously generate superoxide. The second lies in the exquisite susceptibility of NB4 cells to arsenic trioxide-induced, reactive oxygen species (ROS)-mediated apoptosis due to less efficiency of the cellular defense system. In this study, we demonstrated that sodium selenite could induce apoptosis in NB4 cells via the classic mitochondrial pathway involving caspase-3 activation and Bcl-2 cleavage. An increase in the basal cellular **glutathione** (GSH) content rendered NB4 cells resistant to arsenic trioxide, but could sensitize NB4 cells to sodium selenite. Moreover, combined treatment of NB4 cells with all- trans retinoic acid (ATRA) at low concentration and sodium selenite exhibited a synergistic effect on apoptosis induction. Together, our results suggest that selenite is a promising candidate for treatment of acute promyelocytic leukemia (APL) and the mechanism underlying its **anticancer** effects warrants further investigation.

L38 ANSWER 9 OF 67 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004141888 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14988435
TITLE: **Glutathione** metabolism and its implications for health.
AUTHOR: Wu Guoyao; Fang Yun-Zhong; Yang Sheng; Lupton Joanne R; Turner Nancy D
CORPORATE SOURCE: Faculty of Nutrition, Texas A&M University, College Station, TX, 77843, USA.. g-wu@tamu.edu
CONTRACT NUMBER: P30-ES09106 (NIEHS)
R01CA61750 (NCI)
SOURCE: Journal of nutrition, (2004 Mar) 134 (3) 489-92. Ref: 31
Journal code: 0404243. ISSN: 0022-3166.
(Investigators: Lupton J R, TX A&M U, College Station)
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200404

ENTRY DATE: Entered STN: 20040324
Last Updated on STN: 20040420
Entered Medline: 20040419

AB **Glutathione** (gamma-glutamyl-cysteinyl-glycine; GSH) is the most abundant low-molecular-weight **thiol**, and GSH/**glutathione** disulfide is the major **redox** couple in animal cells. The synthesis of GSH from glutamate, cysteine, and glycine is catalyzed sequentially by two cytosolic enzymes, gamma-glutamylcysteine synthetase and GSH synthetase. Compelling evidence shows that GSH synthesis is regulated primarily by gamma-glutamylcysteine synthetase activity, cysteine availability, and GSH feedback inhibition. Animal and human studies demonstrate that adequate protein nutrition is crucial for the maintenance of GSH homeostasis. In addition, enteral or parenteral cystine, methionine, N-acetyl-cysteine, and L-2-oxothiazolidine-4-carboxylate are effective precursors of cysteine for tissue GSH synthesis. **Glutathione** plays important roles in antioxidant defense, nutrient metabolism, and regulation of cellular events (including gene expression, DNA and protein synthesis, cell **proliferation** and apoptosis, signal transduction, cytokine production and immune response, and protein glutathionylation). **Glutathione** deficiency contributes to oxidative stress, which plays a key role in aging and the pathogenesis of many diseases (including kwashiorkor, seizure, Alzheimer's disease, Parkinson's disease, liver disease, cystic fibrosis, sickle cell anemia, HIV, AIDS, **cancer**, heart attack, stroke, and diabetes). New knowledge of the nutritional regulation of GSH metabolism is critical for the development of effective strategies to improve health and to treat these diseases.

L38 ANSWER 10 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2003423750 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12796500
TITLE: A 16-residue peptide fragment of macrophage migration inhibitory factor, MIF-(50-65), exhibits **redox** activity and has MIF-like biological functions.
AUTHOR: Nguyen Mai Tuyet; Beck Jurgen; Lue Hongqi; Funfzig Helge; Kleemann Robert; Koolwijk Pieter; Kapurniotu Aphrodite; Bernhagen Jurgen
CORPORATE SOURCE: Division of Biochemistry and Molecular Cell Biology, Institute of Biochemistry, University Hospital RWTH Aachen, D-52074 Aachen, Germany.
SOURCE: Journal of biological chemistry, (2003 Sep 5) 278 (36) 33654-71. Electronic Publication: 2003-06-09.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030911
Last Updated on STN: 20031008
Entered Medline: 20031007

AB Macrophage migration inhibitory factor (MIF) is a cytokine that participates in the host inflammatory response. A Cys-Xaa-Xaa-Cys (CXXC)-based **thiol**-protein oxidoreductase activity of MIF is associated with certain biological functions. Peptides spanning the CXXC region of **thiol**-protein oxidoreductases retain some biochemical properties of the full-length protein. We report on the characterization of CXXC-spanning MIF-(50-65) and its serine variant, C57S/C60S-MIF-(50-65). Following disulfide-mediated cyclization, MIF-(50-65) adapted a

beta-turn conformation comparable with that of beta-turn-containing cyclo-57,60-[Asp57,Dap60]MIF-(50-65). MIF-(50-65) had a **redox** potential E'0 of -0.258 V and formed mixed disulfides with **glutathione** and cysteine. MIF-(50-65) but not C57S/C60S-MIF-(50-65) had oxidoreductase activity in vitro. Intriguingly, MIF-(50-65) exhibited MIF-like cellular activities. The peptide but not its variant had glucocorticoid overriding and **proliferation** -enhancing activity and stimulated ERK1/2 phosphorylation. MIF-(50-65) and its variant bound to the MIF-binding protein JAB1 and enhanced cellular levels of p27Kip1. As the peptide and its variant were endocytosed at similar efficiency, sequence 50-65 appears sufficient for the JAB1-related effects of MIF, whereas other activities require CXXC. Cyclo-57,60-[Asp57,Dap60]MIF-(50-65) activated ERK1/2, indicating that CXXC-dependent disulfide and beta-turn formation is associated with an activity-inducing conformation. We conclude that CXXC and sequence 50-65 are critical for the activities of MIF. MIF-(50-65) is a surprisingly short sequence with MIF-like functions that could be an excellent molecular template for MIF therapeutics.

L38 ANSWER 11 OF 67 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003197407 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12574159
TITLE: Rapid induction of cell death by selenium-compromised **thioredoxin** reductase 1 but not by the fully active enzyme containing selenocysteine.
AUTHOR: Anestal Karin; Arner Elias S J
CORPORATE SOURCE: Medical Nobel Institute for Biochemistry, Department of Medical Biochemistry and Biophysics, Karolinska Institute, 171 77 Stockholm, Sweden.
SOURCE: Journal of biological chemistry, (2003 May 2) 278 (18) 15966-72. Electronic Publication: 2003-02-06.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030429
Last Updated on STN: 20030618
Entered Medline: 20030617

AB Mammalian **thioredoxin** reductases are selenoproteins. For native catalytic activity, these enzymes utilize a C-terminal -Gly-Cys-Sec-Gly-COOH sequence (where Sec is selenocysteine) forming a **redox** active selenenylsulfide/**selenolthiol** motif. A range of cellular systems depend upon or are regulated by **thioredoxin** reductase and its major protein substrate **thioredoxin**, including apoptosis signal-regulating kinase 1, **peroxiredoxins**, methionine sulfoxide reductase, and several transcription factors. Cytosolic **thioredoxin** reductase 1 (TrxR1) is moreover inhibited by various electrophilic **anticancer** compounds. TrxR1 is hence generally considered to promote cell viability. However, several recent studies have suggested that TrxR1 may promote apoptosis, and the enzyme was identified as GRIM-12 (gene associated with retinoid interferon-induced mortality 12). Transient transfection with GRIM-12/TrxR1 was also shown to directly induce cell death. To further analyze such effects, we have here employed lipid-mediated delivery of recombinant TrxR1 preparations into human A549 cells, thereby bypassing selenoprotein translation to facilitate assessment of the protein-related effects on cell viability. We found that selenium-deficient TrxR1, having

a two-amino acid-truncated C-terminal -Gly-Cys-COOH motif, rapidly induced cell death (38 +/- 29% apoptotic cells after 4 h; p < 0.005 compared with controls). Cell death induction was also promoted by selenium-compromised TrxR1 derivatized with either cis-diamminedichloroplatinum (II) (cisplatin) or dinitrophenyl moieties but not by the structurally related non-selenoprotein **glutathione** reductase. In contrast, TrxR1 with intact selenocysteine could not promote cell death. The direct cellular effects of selenium-compromised forms of TrxR1 may be important for the pathophysiology of selenium deficiency as well as for the efficacy of **antiproliferative** drugs targeting the selenocysteine moiety of this enzyme.

L38 ANSWER 12 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2003119084 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12626594
TITLE: The cytokine macrophage migration inhibitory factor reduces pro-oxidative stress-induced apoptosis.
AUTHOR: Nguyen Mai Tuyet; Lue Hongqi; Kleemann Robert; Thiele Michael; Tolle Gabriele; Finkelmeier Doris; Wagner Eva; Braun Andrea; Bernhagen Jurgen
CORPORATE SOURCE: Laboratory of Biochemistry, Institute for Interfacial Engineering, University of Stuttgart and Fraunhofer Institut fur Grenzflachen-und Bioverfahrenstechnik, Stuttgart, Germany.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2003 Mar 15) 170 (6) 3337-47.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030314
Last Updated on STN: 20030626
Entered Medline: 20030625

AB The cytokine macrophage migration inhibitory factor (MIF) exhibits pro- and anti-inflammatory activities and regulates cell **proliferation** and survival. We investigated the effects of MIF on apoptosis. As MIF exhibits oxidoreductase activity and participates in regulating oxidative cell stress, we studied whether MIF could affect oxidative stress-induced apoptosis. We demonstrated that MIF exhibits antiapoptotic activity in various settings. MIF suppressed camptothecin-induced apoptosis in HeLa and Kym cells and HL-60 promyeloblasts. Both exogenous MIF and endogenous MIF, induced following overexpression through tetracycline (tet) gene induction, led to significant suppression of apoptosis. Apoptosis reduction by MIF was also observed in T cells. A role for MIF in **redox** stress-induced apoptosis was addressed by comparing the effects of rMIF with those of the oxidoreductase mutant C60SMIF. Endogenous overexpression of C60SMIF was similar to that of MIF, but C60SMIF did not suppress apoptosis. Exogenous rC60SMIF inhibited apoptosis. A role for MIF in oxidative stress-induced apoptosis was directly studied in HL-60 leukocytes and tet-regulated HeLa cells following **thiol** starvation or diamide treatment. MIF protected these cells from **redox** stress-induced apoptosis and enhanced cellular **glutathione** levels. As overexpressed C60SMIF did not protect tet-regulated HeLa cells from **thiol** starvation-induced apoptosis, it seems that the **redox** motif of MIF is important for this function. Finally, overexpression of MIF inhibited phosphorylation of endogenous c-Jun induced by **thiol** starvation, indicating that

MIF-based suppression of apoptosis is mediated through modulation of c-Jun N-terminal kinase activity. Our findings show that MIF has potent antiapoptotic activities and suggest that MIF is a modulator of pro-oxidative stress-induced apoptosis.

L38 ANSWER 13 OF 67 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2002730644 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12494466
TITLE: Prostaglandin J2 metabolites inhibit aromatase activity by **redox**-sensitive mechanisms: potential implications for breast **cancer** therapy.
AUTHOR: Winnett Georgia; van Hagen Daphne; Schrey Michael
CORPORATE SOURCE: Endocrinology and Metabolic Medicine, Division of Medicine, Faculty of Medicine, Imperial College of Science Technology and Medicine, London, United Kingdom.
SOURCE: International journal of cancer. Journal international du cancer, (2003 Feb 20) 103 (5) 600-5.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021221
Last Updated on STN: 20030207
Entered Medline: 20030206

AB The mechanisms by which prostaglandin (PG)J(2) metabolites inhibit **tumorigenicity** are poorly understood but may involve **thiol** reactivity or peroxisome **proliferator**-activated receptor (PPAR)-dependent pathways. Because aromatase is an important therapeutic target in breast **cancer** treatment, we have investigated the effect of PGJ(2) metabolites on aromatase activity and evaluated a potential role for **redox** status during PGJ(2) metabolite action. 15-deoxy-Delta(12,14)PGJ(2) (15d-PGJ(2)) and 9-deoxy-Delta(9,12)13,14-dihydroPGD(2) (Delta(12)PGJ(2)) caused dose-dependent inhibition of both pre-induced aromatase activity in human breast fibroblasts and MDA MB 231 breast **cancer** cells and of constitutive aromatase activity in JEG-3 **choriocarcinoma** cells. Structure-activity studies showed that this inhibition was mimicked by 4-cyclopentene-1,3-dione but not by the PPARgamma agonist troglitazone nor the eicosanoids PGE(2) or arachidonic acid. The **thiol** oxidants diamide and H(2)O(2) simulated the inhibitory action of 15d-PGJ(2) on aromatase activity, whereas the **glutathione** (GSH) repletor and antioxidant N-acetyl-cysteine (**NAC**) reversed these actions of 15d-PGJ(2) and H(2)O(2) on aromatase. 15d-PGJ(2) also caused a direct dose-dependent inhibition of aromatase activity in JEG-3 cell sonicates, which was also reversed in the presence of GSH. Kinetic analysis of this 15d-PGJ(2)-induced inhibition of cell-free aromatase indicated the involvement of a non-competitive mechanism possibly resulting from direct **thiol**-targeted alkylation of the enzyme. These **redox**-sensitive, PPARgamma-independent actions of 15d-PGJ(2) on aromatase activity demonstrate a novel therapeutic potential for such cyclopentenone PGs in breast **cancer** treatment.


L38 ANSWER 14 OF 67 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2004006646 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14703721
TITLE: Activation of DNA biosynthesis in human hepatoblastoma

HEPG2 cells by the nitric oxide donor, sodium nitroprusside.
AUTHOR: Sokolowska Maria; Rokita Hanna; Wlodek Lidia
CORPORATE SOURCE: Institute of Medical Biochemistry, Collegium Medicum, Jagiellonian University, 31-034 Cracow, Poland.
SOURCE: Fundamental & clinical pharmacology, (2003 Oct) 17 (5) 599-607.
Journal code: 8710411. ISSN: 0767-3981.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20040106
Last Updated on STN: 20040603
Entered Medline: 20040602

AB The role of nitric oxide (NO) in **carcinogenesis** is controversial as it has been shown to both stimulate and inhibit **tumour** growth. Also, there are contradictory opinions regarding the effects of NO on the **proliferation** of normal and **tumour** cells.
The aim of our study was to use an in vitro model to determine the influence of exogenous NO donors on DNA biosynthesis by measuring [3H] thymidine incorporation in human hepatoblastoma cells (HepG2). The studies were conducted with the following NO precursors: sodium nitroprusside (SNP), S-**nitrosoglutathione**, and nitroglycerine (NTG). Out of all three NO donors, SNP increased NO levels and strongly stimulated DNA biosynthesis. A SNP concentration of 150 microM induced optimal NO levels necessary for the activation of DNA biosynthesis. Lower levels of DNA biosynthesis (118% increase over the control) were observed in the presence of NTG, whereas S-**nitrosoglutathione** had no effect. Antioxidants such as **thiol**-containing drugs, **N** -**acetylcysteine** and tocopherol, proved to be the most efficient co-activators of SNP-induced DNA synthesis. On the other hand, supplementing the SNP-containing medium with compounds that induce oxidative stress and lower the level of -SH groups such as hydrogen peroxide, doxorubicin, and N-ethylmaleimide, led to the inhibition of DNA synthesis. Therefore, our results firmly confirm the hypothesis that biological effects of exogenous NO donors depends on the **redox** status of the cell.

L38 ANSWER 15 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2003528606 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14606649
TITLE: **Redox** modulation of NF-kappaB nuclear translocation and DNA binding in metastatic melanoma. The role of endogenous and gamma-glutamyl transferase-dependent oxidative stress.
AUTHOR: Dominici Silvia; Visvikis Athanase; Pieri Lisa; Paolicchi Aldo; Valentini Marta A; Comporti Mario; Pompella Alfonso
CORPORATE SOURCE: Department of Experimental Pathology, University of Pisa Medical School, Pisa, Italy.
SOURCE: Tumori, (2003 Jul-Aug) 89 (4) 426-33.
Journal code: 0111356. ISSN: 0300-8916.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031111

Last Updated on STN: 20031219
Entered Medline: 20031202

AB AIMS AND BACKGROUND: The transcription factor NF-kappaB is implicated in the expression of genes involved in cell **proliferation**, apoptosis and metastasis. In melanoma, high constitutive levels of NF-kappaB activation are usually observed. NF-kappaB is regulated by oxidation/reduction (**redox**) processes, and the occurrence of constitutive oxidative stress in melanoma cells has been documented. Recent studies of our laboratories showed that the membrane-bound gamma-glutamyl transferase (GGT) enzyme activity--expressed by a number of malignancies, including melanoma--can act as a basal source of superoxide, hydrogen peroxide and other prooxidants. METHODS: In the present study we utilized the 2/60 clone of Me665/2 human metastatic melanoma, which displays high levels of GGT activity, in order to verify if the presence of this enzyme--through the promotion of **redox** processes--may influence the activation status of NF-kappaB. The latter was evaluated by determining the nuclear translocation of the p65 subunit (by immunoblot), the DNA binding of NF-kappaB (by electrophoretic mobility shift assay) and its transcriptional activity (by gene transactivation studies). RESULTS: Me665/2/60 cells displayed a basal production of hydrogen peroxide. Stimulation of GGT activity by its substrates **glutathione** and glycyl-glycine caused additional production of hydrogen peroxide, up to levels approx. double the basal levels. Nuclear translocation of the NF-kappaB p65 subunit, DNA-binding and gene transactivation were thus investigated in Me665/2/60 cells whose GGT activity was modulated by means of substrates or inhibitors. Stimulation of GGT activity resulted in increased nuclear translocation of p65, while on the other hand NF-kappaB DNA binding and gene transactivation were paradoxically decreased. NF-kappaB DNA binding could be restored by treating cell lysates with the **thiol**-reducing agent **dithiothreitol** (DTT). Treatment of cells with exogenous hydrogen peroxide did not affect NF-kappaB activation status. CONCLUSIONS: Altogether, the data obtained indicate that GGT activity may impair the **redox** status of **thiols** that is critical for NF-kappaB DNA binding and gene transactivation, through the production of prooxidant species allegedly distinct from hydrogen peroxide. GGT activity therefore appears to be an additional factor in modulation of NF-kappaB transcriptional activity in melanoma, capable of hindering NF-kappaB DNA binding even in conditions where continuous oxidative stress would favor NF-kappaB nuclear translocation.

L38 ANSWER 16 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003417596 EMBASE
TITLE: **Redox** state of **glutathione** and **thioredoxin** in differentiation and apoptosis.
AUTHOR: Watson W.H.; Chen Y.; Jones D.P.
CORPORATE SOURCE: W.H. Watson, Department of Biochemistry, Emory University School of Medicine, Atlanta, GA, United States
SOURCE: BioFactors, (2003) Vol. 17, No. 1-4, pp. 307-314.
Refs: 29
ISSN: 0951-6433 CODEN: BIFAEU
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 20031030
Last Updated on STN: 20031030

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L38 ANSWER 17 OF 67 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2003051328 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12560100
TITLE: **Redox** catalysts as sensitisers towards oxidative stress.
AUTHOR: Giles Niroshini M; Gutowski Nick J; Giles Gregory I; Jacob Claus
CORPORATE SOURCE: School of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK.
SOURCE: FEBS letters, (2003 Jan 30) 535 (1-3) 179-82.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030202
Last Updated on STN: 20030322
Entered Medline: 20030321
AB The predominance of oxidative stress in many **tumour** cell environments provides a means to selectively target these cells via protein oxidation. The zinc fingers of transcription factors utilise cysteine **thiols** for structural zinc coordination. **Redox** control of DNA binding regulates transcription and therefore the overall rates of **proliferation**, apoptosis and necrosis in the **carcinoma.** We report here the adverse effects of **glutathione** peroxidase (GPx) mimics towards zinc finger motifs and PC12 cell survival. Nanomolar catalyst concentrations facilitated H2O2-induced oxidation of an Sp1 transcription factor fragment. In PC12 cells GPx catalysis triggered a significant increase in cell death, correlating with severity of oxidative stress. As a consequence, we conclude that GPx mimics are potential chemotherapeutic agents.

L38 ANSWER 18 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003486063 EMBASE
TITLE: Glutamine and KGF each regulate extracellular **thiol** /disulfide **redox** and enhance **proliferation** in Caco-2 cells.
AUTHOR: Jonas C.R.; Gu L.H.; Nkabyo Y.S.; Mannery Y.O.; Avissar N.E.; Sax H.C.; Jones D.P.; Ziegler T.R.
CORPORATE SOURCE: T.R. Ziegler, General Clinical Research Center, Emory Univ. Hospital, 1364 Clifton Rd., Atlanta, GA 30322, United States. tzieg01@emory.edu
SOURCE: American Journal of Physiology - Regulatory Integrative and Comparative Physiology, (2003) Vol. 285, No. 6 54-6, pp. R1421-R1429.
Refs: 42
ISSN: 0363-6119 CODEN: AJPRDO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040105
Last Updated on STN: 20040105
AB Glutamine (Gln) and keratinocyte growth factor (KGF) each stimulate

intestinal epithelial cell growth, but regulatory mechanisms are not well understood. We determined whether Gln and KGF alter intra- and extracellular **thiol**/disulfide **redox** pools in Caco-2 cells cultured in oxidizing or reducing cell medium and whether such **redox** variations are a determinant of **proliferative** responses to these agents. Cells were cultured over a physiological range of oxidizing to reducing extracellular **thiol**/disulfide **redox** (E(h)) conditions, obtained by varying cysteine (Cys) and cystine (CySS) concentrations in cell medium. Cell **proliferation** was determined by 5-bromo-2-deoxyuridine (BrdU) incorporation. Gln (10 mmol/l) or KGF (10 μg/l) did not alter BrdU incorporation at reducing E(h) (-131 to -150 mV), but significantly increased incorporation at more oxidizing E (h) (Gln at 0 to - 109 mV; KGF at -46 to -80 mV). Cellular **glutathione/glutathione** disulfide (GSH/GSSG) E(h) was unaffected by Gln, KGF, or variations in extracellular Cys/CySS E(h). Control cells largely maintained extracellular E(h) at initial values after 24 h (-36 to -136 mV). However, extracellular E(h) shifted toward a narrow physiological range with Gln and KGF treatment (Gln -56 to -88 mV and KGF -76 to -92 mV, respectively; $P < 0.05$ vs. control). The results indicate that **thiol**/disulfide **redox** state in the extracellular milieu is an important determinant of Caco-2 cell **proliferation** induced by Gln and KGF, that this control is independent of intracellular GSH **redox** status, and that both Gln and KGF enhance the capability of Caco-2 cells to modulate extremes of extracellular **redox.**

L38 ANSWER 19 OF 67 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2002409353 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12163679
TITLE: Oxidation of the **glutathione/glutathione** disulfide **redox** state is induced by cysteine deficiency in human colon **carcinoma** HT29 cells.
AUTHOR: Miller Lauren T; Watson Walter H; Kirlin Ward G; Ziegler Thomas R; Jones Dean P
CORPORATE SOURCE: Department of Biochemistry, Emory University School of Medicine, Atlanta, GA 30322, USA.
CONTRACT NUMBER: DK55850 (NIDDK)
ES011195 (NIEHS)
ES09047 (NIEHS)
SOURCE: Journal of nutrition, (2002 Aug) 132 (8) 2303-6.
Journal code: 0404243. ISSN: 0022-3166.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20030312
Entered Medline: 20020904

AB **Glutathione** (GSH) has a central role in the maintenance of the **thiol**-disulfide **redox** state in mammalian cells. GSH synthesis can be physiologically limited by the availability of cysteine (Cys), and Cys and its precursors are variable in the human diet. The purpose of this study was to determine the effect of severe Cys deficiency and readdition of Cys on the **redox** state of the GSH/**glutathione** disulfide (GSSG) pool in human colon **carcinoma** HT29 cells. Cells were cultured in Cys- (and cystine-)limiting medium for 48 h followed by culture in medium containing either Cys or cystine for 24 h. GSH and GSSG were measured by HPLC. Cys limitation decreased cellular

GSH and GSSG concentrations with an associated >80 mV oxidation of the GSH/GSSG **redox** state. Upon addition of either Cys or its disulfide cystine (CySS), **redox** of GSH/GSSG recovered in 4 h, whereas GSH concentration continued to increase over 12 h. Maximal GSH concentrations attained were 200% of control cell values. These results show that severe Cys deficiency can have marked effects on cellular **redox** state but that **redox** recovers rapidly upon resupply. The magnitude of oxidation during Cys limitation in this cell model is sufficient to result in a >100-fold change in the reduced/oxidized ratio of **redox**-sensitive **dithiol** /disulfide motifs in proteins. If **redox** changes occur in vivo in association with variations in dietary Cys and its precursors, these changes could have important physiologic effects through altered **redox** signaling and control of cell **proliferation** and apoptosis.

L38 ANSWER 20 OF 67 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2002687773 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12446207
TITLE: Extracellular **thiol**/disulfide **redox** state affects **proliferation** rate in a human colon **carcinoma** (Caco2) cell line.
AUTHOR: Jonas Carolyn R; Ziegler Thomas R; Gu Li H; Jones Dean P
CORPORATE SOURCE: Department of Biochemistry, Emory University School of Medicine, Atlanta, GA, USA.
CONTRACT NUMBER: M01 RR00039 (NCRR)
R01 ES011195 (NIEHS)
R01 ES09047 (NIEHS)
R01DK55850 (NIDDK)
T32DK07732 (NIDDK)
SOURCE: Free radical biology & medicine, (2002 Dec 1) 33 (11) 1499-506.
Journal code: 8709159. ISSN: 0891-5849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20030529
Entered Medline: 20030528

AB **Redox** mechanisms function in regulation of cell growth, and variation in **redox** state of plasma **thiol**/disulfide couples occurs in various physiologic conditions, including diabetes, chemotherapy, and aging. The present study was designed to determine whether a systematic variation in extracellular **thiol**/disulfide **redox** state (E(h)) over a range (0 mV to -150 mV) that occurs in human plasma altered **proliferation** of cultured cells. Experiments were performed with a human colon **carcinoma** cell line (Caco2), which grows slowly in the absence of serum and responds to peptide growth factors with increased rate of cell division. The extracellular **redox** states were established by varying concentrations of cysteine and cystine, maintaining constant pool size in terms of cysteine equivalents. Incorporation of 5-bromo-2-deoxyuridine (BrdU) was used to measure DNA synthesis and was lowest at the most oxidized extracellular E(h) (0 mV). Incorporation increased as a function of **redox** state, attaining a 100% higher value at the most reduced condition (-150 mV). Addition of insulin-like growth factor-1 (IGF-1) or epidermal growth factor (EGF) increased the rate of BrdU

incorporation at more oxidizing **redox** conditions (0 to -80 mV) but had no effect at -150 mV. Cellular GSH was not significantly affected by variation in extracellular E(h). In the absence of growth factors, extracellular E(h) values were largely maintained for 24 h. However, IGF-1 or EGF stimulated a change in extracellular **redox** to values similar to that for cysteine/cystine **redox** in plasma of young, healthy individuals. The results show that extracellular **thiol**/disulfide **redox** state modulates cell **proliferation** rate and that this control interacts with growth factor signaling apparently independently of cellular **glutathione** .

L38 ANSWER 21 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2002672874 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12433666
TITLE: **Glutathione** and **thioredoxin** **redox** during differentiation in human colon epithelial (Caco-2) cells.
AUTHOR: Nkabyo Yvonne S; Ziegler Thomas R; Gu Li H; Watson Walter H; Jones Dean P
CORPORATE SOURCE: Department of Biochemistry, the Graduate Program in Molecular and Systems Pharmacology, Emory University, Atlanta, Georgia 30322, USA.
CONTRACT NUMBER: DK-55850 (NIDDK)
ES-009047 (NIEHS)
ES-011195 (NIEHS)
RR-00039 (NCRR)
SOURCE: American journal of physiology. Gastrointestinal and liver physiology, (2002 Dec) 283 (6) G1352-9. Journal code: 100901227. ISSN: 0193-1857.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021116
Last Updated on STN: 20021218
Entered Medline: 20021213

AB Cellular **redox**, maintained by the **glutathione** (GSH)- and **thioredoxin** (Trx)-dependent systems, has been implicated in the regulation of a variety of biological processes. The **redox** state of the GSH system becomes oxidized when cells are induced to differentiate by chemical agents. The aim of this study was to determine the **redox** state of cellular GSH/**glutathione** disulfide (GSH/GSSG) and Trx as a consequence of progression from **proliferation** to contact inhibition and spontaneous differentiation in colon **carcinoma** (Caco-2) cells. Results showed a significant decrease in GSH concentration, accompanied by a 40-mV oxidation of the cellular GSH/GSSG **redox** state and a 28-mV oxidation of the extracellular cysteine/cystine **redox** state in association with confluency and increase in differentiation markers. The **redox** state of Trx did not change. Thus the two central cellular antioxidant and **redox**-regulating systems (GSH and Trx) were independently controlled. According to the Nernst equation, a 30-mV oxidation is associated with a 10-fold change in the reduced/oxidized ratio of a **redox**-sensitive **dithiol** motif. Therefore, the measured 40-mV oxidation of the cellular GSH/GSSG couple or the 28-mV oxidation of the extracellular cysteine/cystine couple should be sufficient to function in signaling or regulation of differentiation in

Caco-2 cells.

L38 ANSWER 22 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002384053 EMBASE
TITLE: **Glutathione** catabolism as a signaling mechanism.
AUTHOR: Paolicchi A.; Dominici S.; Pieri L.; Maellaro E.; Pompella A.
CORPORATE SOURCE: A. Pompella, Department of Experimental Pathology, University of Pisa Medical School, Via Roma 55, 56126 Pisa, Italy. apompella@biomed.unipi.it
SOURCE: Biochemical Pharmacology, (1 Sep 2002) Vol. 64, No. 5-6, pp. 1027-1035.
Refs: 38
ISSN: 0006-2952 CODEN: BCPCA6
PUBLISHER IDENT.: S 0006-2952(02)01173-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20021121
Last Updated on STN: 20021121
AB **Glutathione** (GSH) is the main intracellular **thiol** antioxidant, and as such participates in a number of cellular antitoxic and defensive functions. Nevertheless, non-antioxidant functions of GSH have also been decribed, e.g. in modulation of cell **proliferation** and immune response. Recent studies from our and other laboratories have provided evidence for a third functional aspect of GSH, i.e. the prooxidant roles played by molecular species originating during its catabolism by the membrane ectoenzyme γ-glutamyl transpeptidase (GGT). The reduction of metal ions effected by GSH catabolites is capable to induce **redox** cycling processes leading to the production of reactive oxygen species (superoxide, hydrogen peroxide), as well as of other free radicals. Through the action of these reactive compounds, GSH catabolism can ultimately lead to oxidative modifications on a variety of molecular targets, involving oxidation and/or S-**thiolation** of protein **thiol** groups in the first place. Modulating effects of this kind have been observed on several important, **redox** -sensitive components of the signal transduction chains, such as cell surface receptors, protein phosphatase activities and transcription factors. Against this background, the prooxidant reactions induced by GSH catabolism appear to represent a novel, as yet unrecognized mechanism for modulation of cellular signal transduction. .COPYRGT. 2002 Elsevier Science Inc. All rights reserved.

L38 ANSWER 23 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002172879 EMBASE
TITLE: Dendritic cells generate **thiols** for T-cell **proliferation.**
AUTHOR: Keenihan S.H.
CORPORATE SOURCE: keenihan@namru2.med.navy.mil
SOURCE: Trends in Immunology, (1 May 2002) Vol. 23, No. 5, pp. 233.
Refs: 1
ISSN: 1471-4906 CODEN: TIRMAE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 026 Immunology, Serology and Transplantation

037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 20020530
Last Updated on STN: 20020530
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L38 ANSWER 24 OF 67 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2002141305 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11849044
TITLE: Inhibition of cell **proliferation** and AP-1 activity by acrolein in human A549 lung **adenocarcinoma** cells due to **thiol** imbalance and covalent modifications.
AUTHOR: Biswal Shyam; Acquaah-Mensah George; Datta Kaushik; Wu Xuli; Kehrer James P
CORPORATE SOURCE: Bloomberg School of Public Health, Johns Hopkins University, Department of Environmental Health Sciences, Division of Toxicological Sciences, Baltimore, Maryland 21205-2179, USA.. sbiswal@jhsph.edu
CONTRACT NUMBER: ES09791 (NIEHS)
F32 ES05896 (NIEHS)
SOURCE: Chemical research in toxicology, (2002 Feb) 15 (2) 180-6.
Journal code: 8807448. ISSN: 0893-228X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020307
Last Updated on STN: 20020424
Entered Medline: 20020423

AB Acrolein, a reactive alpha,beta-unsaturated aldehyde, is a common environmental pollutant, a metabolite of the **anticancer** drug cyclophosphamide, and a byproduct of lipid peroxidation. An increase in acrolein production has been proposed as a marker for Alzheimer's disease, diabetic glomerular lesions, and atherosclerosis. Acrolein is a potent inhibitor of cell **proliferation** at nonlethal doses and may act through effects on **redox**-regulated transcription factors. We previously reported that NF-kappaB activation is inhibited by acrolein in the A549 lung **adenocarcinoma** cell line in an IkappaB-independent manner [Horton et al. (1999) J. Biol. Chemical 274, 9200-9206]. The current data demonstrate that AP-1 activation in A549 cells is decreased by 26 and 50% at 0.5 and 1 h, respectively, after exposure to 50 fmol/cell (a nonlethal dose) of acrolein. Inhibition of AP-1 activation also occurred following treatment with **buthionine sulfoximine** to deplete **glutathione** to the same extent as seen with acrolein. c-jun antisense treatments depressed c-jun protein below detectable levels at 4 h and inhibited cell **proliferation** (as assessed by [(3)H]thymidine incorporation) by 80%. Immunoprecipitation of c-jun protein after treating A549 cells with acrolein revealed the presence of a lysine-acrolein adduct. There was, however, no effect of acrolein on c-jun N-terminal kinase activity or c-jun phosphorylation. These data indicate that the inhibition of cell **proliferation** induced by acrolein correlates with the depletion of **glutathione** as well as the inhibition of AP-1 activation. AP-1 activation is likely affected both through changes in cellular **thiol redox** balance and by covalent modification of acrolein to c-jun, but not through effects on c-jun phosphorylation.

L38 ANSWER 25 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002421555 EMBASE
TITLE: **Glutathione** and **thioredoxin** **redox** during differentiation in human colon epithelial (Caco-2) cells.
AUTHOR: Nkabyo Y.S.; Ziegler T.R.; Gu L.H.; Watson W.H.; Jones D.P.
CORPORATE SOURCE: D.P. Jones, Dept. of Biochemistry, Rollins Research Center, Emory University, 1510 Clifton Rd. NE, Atlanta, GA 30322, United States. dpjones@emory.edu
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (1 Dec 2002) Vol. 283, No. 6 46-6, pp. G1352-G1359.
Refs: 39
ISSN: 0193-1857 CODEN: APGPDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20021212
Last Updated on STN: 20021212

AB Cellular **redox**, maintained by the **glutathione** (GSH)- and **thioredoxin** (Trx)-dependent systems, has been implicated in the regulation of a variety of biological processes. The **redox** state of the GSH system becomes oxidized when cells are induced to differentiate by chemical agents. The aim of this study was to determine the **redox** state of cellular GSH/**glutathione** disulfide (GSH/GSSG) and Trx as a consequence of progression from **proliferation** to contact inhibition and spontaneous differentiation in colon **carcinoma** (Caco-2) cells. Results showed a significant decrease in GSH concentration, accompanied by a 40-mV oxidation of the cellular GSH/GSSG **redox** state and a 28-mV oxidation of the extracellular cysteine/cystine **redox** state in association with confluency and increase in differentiation markers. The **redox** state of Trx did not change. Thus the two central cellular antioxidant and **redox**-regulating systems (GSH and Trx) were independently controlled. According to the Nernst equation, a 30-mV oxidation is associated with a 10-fold change in the reduced/oxidized ratio of a **redox**-sensitive **dithiol** motif. Therefore, the measured 40-mV oxidation of the cellular GSH/GSSG couple or the 28-mV oxidation of the extracellular cysteine/cystine couple should be sufficient to function in signaling or regulation of differentiation in Caco-2 cells.

L38 ANSWER 26 OF 67 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2001287563 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11278531
TITLE: Cyclopentenone prostaglandins as potential inducers of intracellular oxidative stress.
AUTHOR: Kondo M; Oya-Ito T; Kumagai T; Osawa T; Uchida K
CORPORATE SOURCE: Laboratory of Food and Biodynamics, Graduate School of Bioagricultural Sciences, Nagoya University, Nagoya 464-8601, Japan.
SOURCE: Journal of biological chemistry, (2001 Apr 13) 276 (15) 12076-83. Electronic Publication: 2001-01-12.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20030105
Entered Medline: 20010524

AB In the present study, we find that cyclopentenone prostaglandins (PGs) of the J(2) series, naturally occurring derivatives of PGD(2), are potential inducers of intracellular oxidative stress that mediates cell degeneration. Based on an extensive screening of diverse chemical agents on induction of intracellular production of reactive oxygen species (ROS), we found that the cyclopentenone PGs, such as PGA(2), PGJ(2), Delta(12)-PGJ(2), and 15-deoxy-Delta(12,14)-PGJ(2), showed the most potent pro-oxidant effect on SH-SY5Y human neuroblastoma cells. As the intracellular events that mediate the PG cytotoxicity, we observed (i) the cellular **redox** alteration represented by depletion of antioxidant defenses, such as **glutathione** and **glutathione** peroxidase; (ii) a transient decrease in the mitochondrial membrane potential (Deltapsi); (iii) the production of protein-bound lipid peroxidation products, such as acrolein and 4-hydroxy-2-nonenal; and (iv) the accumulation of ubiquitinated proteins. These events correlated well with the reduction in cell viability. In addition, the **thiol** compound, **N-acetylcysteine**, could significantly inhibit the PG-induced ROS production, thereby preventing cytotoxicity, suggesting that the **redox** alteration is closely related to the pro-oxidant effect of cyclopentenone PGs. More strikingly, the lipid peroxidation end products, acrolein and 4-hydroxy-2-nonenal, detected in the PG-treated cells potently induced the ROS production, which was accompanied by the accumulation of ubiquitinated proteins and cell death, suggesting that the membrane lipid peroxidation products may represent one of the causative factors that potentiate the cytotoxic effect of cyclopentenone PGs by accelerating intracellular oxidative stress. These data suggest that the intracellular oxidative stress, represented by ROS production/lipid peroxidation and **redox** alteration, may underlie the well documented biological effects, such as **antiproliferative** and **antitumor** activities, of cyclopentenone PGs.

L38 ANSWER 27 OF 67 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 2001111315 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11123355
TITLE: Cellular **thiols** and reactive oxygen species in drug-induced apoptosis.
AUTHOR: Davis W Jr; Ronai Z; Tew K D
CORPORATE SOURCE: Department of Pharmacology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA.
CONTRACT NUMBER: CA06927 (NCI)
CA85660 (NCI)
RR05539 (NCRR)
SOURCE: Journal of pharmacology and experimental therapeutics, (2001 Jan) 296 (1) 1-6. Ref: 43
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010202

AB In higher eukaryotes, reactive oxygen species (ROS) are generated during respiration in mitochondria in the course of reduction of molecular oxygen as well as by distinct enzyme systems. ROS have been implicated in the regulation of diverse cellular functions including defense against pathogens, intracellular signaling, transcriptional activation, **proliferation**, and apoptosis. The reduction-oxidation ( **redox**) state of the cell is primarily a consequence of the precise balance between the levels of ROS and endogenous **thiol** buffers present in the cell, such as **glutathione** and **thioredoxin** , which protect cells from oxidative damage. Dramatic elevation of ROS, exceeding compensatory changes in the level of the endogenous **thiol** buffers, may result in the sustained activation of signaling pathways and expression of genes that induce apoptosis in affected cells. Many cytotoxic drugs function selectively to kill **cancer** cells by the abrogation of **proliferative** signals, leading to cell death, and numerous reports have demonstrated that ROS are generated following treatment with these drugs. In this review, we will summarize recent contributions to our understanding of the importance of cytotoxic drug-induced modulation of cellular **redox** status for signaling and transcription leading to activation of apoptotic effector mechanisms.

L38 ANSWER 28 OF 67 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2001040936 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11029606
TITLE: Virological and immunological effects of antioxidant treatment in patients with HIV infection.
AUTHOR: Muller F; Svardal A M; Nordoy I; Berge R K; Aukrust P; Froland S S
CORPORATE SOURCE: University of Oslo, The National Hospital, Rikshospitalet, Oslo, Norway.. fredrik.muller@labmed.uio.no
SOURCE: European journal of clinical investigation, (2000 Oct) 30 (10) 905-14.
Journal code: 0245331. ISSN: 0014-2972.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207

AB BACKGROUND: Intracellular oxidative stress in CD4+ lymphocytes due to disturbed **glutathione** homeostasis may lead to impaired lymphocyte functions and enhanced HIV replication in patients with HIV infection, especially in those with advanced immunodeficiency. The aim of the present study was to assess whether short-term, high-dose antioxidant treatment might have effects on immunological and virological parameters in patients with HIV infection. MATERIALS AND METHODS: In this pilot study, we examined virological and immunological effects of antioxidant combination treatment for 6 days with high doses of **N-acetylcysteine** (**NAC**) and vitamin C in 8 patients with HIV infection. The following were assayed before, during and after antioxidant treatment: HIV RNA plasma levels; numbers of CD4+, CD8+, and CD14+ leukocytes in blood; plasma **thiols**; intracellular

**glutathione redox** status in CD4+ lymphocytes and CD14+ monocytes; lymphocyte **proliferation**; lymphocyte apoptosis and plasma levels of **tumour** necrosis factor (TNF)alpha; soluble TNF receptors and neopterin in plasma. RESULTS: No significant changes in HIV RNA plasma levels or CD4+ lymphocyte counts in blood were noted during antioxidant treatment in the patient group. However, in the 5 patients with the most advanced immunodeficiency (CD4+ lymphocyte counts < 200 x 106 L(-1)), a significant rise in CD4+ lymphocyte count, a reduction in HIV RNA plasma level of 0.8 log, an enhanced lymphocyte **proliferation** and an increased level of intracellular **glutathione** in CD4+ lymphocytes were found. No change in lymphocyte apoptosis was noted. CONCLUSIONS: Short-term, high-dose combination treatment with **NAC** and vitamin C in patients with HIV infection and advanced immunodeficiency lead to immunological and virological effects that might be of therapeutic value.

L38 ANSWER 29 OF 67 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 1999418846 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10490284
TITLE: **Redox** modulation of cell surface protein **thiols** in U937 lymphoma cells: the role of gamma-glutamyl transpeptidase-dependent H2O2 production and S-**thiolation.**
AUTHOR: Dominici S; Valentini M; Maellaro E; Del Bello B; Paolicchi A; Lorenzini E; Tongiani R; Comporti M; Pompella A
CORPORATE SOURCE: Institute of General Pathology, University of Siena, Italy.
SOURCE: Free radical biology & medicine, (1999 Sep) 27 (5-6) 623-35.
Journal code: 8709159. ISSN: 0891-5849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991019

AB The expression of gamma-glutamyl transpeptidase (GGT), a plasma membrane ectoenzyme involved in the metabolism of extracellular reduced **glutathione** (GSH), is a marker of **neoplastic** progression in several experimental models, and occurs in a number of human malignant **neoplasms** and their metastases. Because it favors the supply of precursors for the synthesis of GSH, GGT expression has been interpreted as a member in cellular antioxidant defense systems. However, **thiol** metabolites generated at the cell surface during GGT activity can induce prooxidant reactions, leading to production of free radical oxidant species. The present study was designed to characterize the prooxidant reactions occurring during GGT ectoactivity, and their possible effects on the **thiol redox** status of proteins of the cell surface. Results indicate that: (i) in U937 cells, expressing significant amounts of membrane-bound GGT, GGT-mediated metabolism of GSH is coupled with the extracellular production of hydrogen peroxide; (ii) GGT activity also results in decreased levels of protein **thiols** at the cell surface; (iii) GGT-dependent decrease in protein **thiols** is due to sulfhydryl oxidation and protein S-**thiolation** reactions; and (iv) GGT irreversible inhibition by **acivicin** is sufficient to produce an increase of protein **thiols** at the cell surface. Membrane receptors and transcription factors have been shown to possess critical **thiols** involved in

the transduction of **proliferative** signals. Furthermore, it was suggested that S-**thiolation** of cellular proteins may represent a mechanism for protection of vulnerable **thiols** against irreversible damage by prooxidant agents. Thus, the findings reported here provide additional explanations for the envisaged role played by membrane-bound GGT activity in the **proliferative** attitude of malignant cells and their resistance to prooxidant drugs and radiation therapy.

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ACCESSION NUMBER: 1999010471 EMBASE
TITLE: Changes in **glutathione** status and the antioxidant system in blood and in **cancer** cells associate with **tumour** growth in vivo.
AUTHOR: Navarro J.; Obrador E.; Carretero J.; Petschen I.; Avino J.; Perez P.; Estrela J.M.
CORPORATE SOURCE: Dr. J.M. Estrela, Departamento de Fisiologia, Facultad de Medicina, Av. Biasco Ibanez 17, 46010 Valen, Spain. jose.mlestrela@uv.es
SOURCE: Free Radical Biology and Medicine, (**1999**) Vol. 26, No. 3-4, pp. 410-415.
Refs: 47
ISSN: 0891-5849 CODEN: FRBMEH
PUBLISHER IDENT.: S 0891-5849(98)00213-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19990204
Last Updated on STN: 19990204

AB The relationship among **cancer** growth, the **glutathione redox** cycle and the antioxidant system was studied in blood and in **tumour** cells. During **cancer** growth, the **glutathione redox** status (GSH/GSSG) decreases in blood of Ehrlich ascites **tumour**-bearing mice. This effect is mainly due to an increase in GSSG levels. Two reasons may explain the increase in blood GSSG: (a) the increase in peroxide production by the **tumour** that, in addition to changes affecting the **glutathione**-related and the antioxidant enzyme activities, can lead to GSH oxidation within the red blood cells; and (b) an increase of GSSG release from different tissues into the blood. GSH and peroxide levels are higher in the **tumour** cells when they **proliferate** actively, however GSSG levels remain constant during turnout growth in mice. These changes associate with low levels of lipid peroxidation in plasma, blood and the **tumour** cells. The GSH/GSSG ratio in blood also decreases in patients bearing breast or colon **cancers** and, as it occurs in **tumour**-bearing mice, this change associates with higher GSSG levels, especially in advanced stages of **cancer** progression. Our results indicate that determination of **glutathione** status and oxidative stress-related parameters in blood may help to orientate **cancer** therapy in humans.

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ACCESSION NUMBER: 1999213264 EMBASE

TITLE: Induction of **thioredoxin** by oxidative stress and overexpression of **thioredoxin** in lung **cancer** tissue.

AUTHOR: Jang Hoon Lee; Hyung Jung Kim; Chul Min Ahn; Sung Kyu Kim; Won Young Lee

CORPORATE SOURCE: Dr. J.H. Lee, Department of Internal Medicine, Yonsei Univ. College of Medicine, Seoul, Korea, Republic of

SOURCE: Tuberculosis and Respiratory Diseases, (**1999**) Vol. 46, No. 3, pp. 327-337.
Refs: 32
ISSN: 0378-0066 CODEN: KHCHAM

COUNTRY: Korea, Republic of

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index

LANGUAGE: Korean

SUMMARY LANGUAGE: English; Korean

ENTRY DATE: Entered STN: 19990708
Last Updated on STN: 19990708

AB Background: Reactive oxygen species are involved in multi-stage process of **carcinogenesis.** The most of **cancer** cell lines and **cancer** cells in **tumor** tissue produce reactive oxygen species and on the other hand, the activities of catalase, Mn- and CuZn-superoxide dismutase in **tumor** cells are usually low. These persistent oxidative stress in **tumor** tissue facilitates **tumor** invasion and metastasis. 12-kDa **thioredoxin**, which regulates the intracellular **redox** potential with **glutathione** and **glutaredoxin** is involved in cell activation, **proliferation**, differentiation and **redox** -mediated apoptosis. It is also purified as 14-kDa and 10-kDa eosinophilic cytotoxic enhancing factor(ECEF) from human histiocytic cell(U937) and 10-kDa ECEF has more than 20 times eosinophilic stimulation activity than 14-kDa ECEF. It has been reported that adult T-cell leukemia, squamous cell **carcinoma** of uterine cervix, and hepatocellular **carcinoma** show increased amounts of human **thioredoxin** and **thioredoxin** mRNA is increased in lung **cancer.** In this study, we investigated the expression of conventional antioxidant enzymes such as catalase, CuZn-SOD, and **glutathione** peroxidase and **thioredoxin** in lung **cancer** tissue compared to adjacent normal lung tissue and the induction of **thioredoxin** in macrophage cells after treatment of oxidative stress and endotoxin. Methods: We measured the amount of conventional antioxidant enzymes such as catalase, CuZn-SOD, and **glutathione** peroxidase and **thioredoxin** in lung **cancer** tissue compared to adjacent normal lung tissue by immunoblot analysts and the induction of **thioredoxin** in mouse monocyte- macrophage cells(RAW 264.7) by treatment of 5 μM menadione and 1 μg/ml endotoxin. Results: On immunoblot analysis, the expression of 12-kDa **thioredoxin** was increased in lung **cancer** tissue compared to paired normal lung tissue, but the expression of catalase and CuZn-SOD were decreased in lung **cancer** tissue compared to paired normal tissue and the expression of **glutathione** peroxidase in lung **cancer** was variable. The expression of truncated **thioredoxin** was also increased in lung **cancer** . When mouse monocyte- macrophage cells were treated with 5 μM menadione and 1 μg/ml endotoxin, the expression of **thioredoxin** was peaked at 12 hrs and sustained to 48 hrs. Conclusion: In contrast with other conventional antioxidants, the expression of 12-kDa and

truncated **thioredoxin** in lung **cancer** were increased and it is closely associated with persistent oxidative stress in **tumor** microenvironment. Considering especially the biological functions of truncated **thioredoxin**, the increased amount of truncated **thioredoxin** has significant role in **tumor** growth through cell **proliferation.**

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ACCESSION NUMBER: 1999419649 EMBASE
TITLE: Increased **glutathione** synthesis associated with platelet-derived growth factor stimulation of NIH3T3 fibroblasts.
AUTHOR: Iantomasi T.; Favilli F.; Degl'Innocenti D.; Vincenzini M.T.
CORPORATE SOURCE: M.T. Vincenzini, Department of Biochemical Sciences, University of Florence, viale Morgagni 50, 50134 Florence, Italy. vincenzini@cesit1.unifi.it
SOURCE: Biochimica et Biophysica Acta - Molecular Cell Research, (**1999**) Vol. 1452, No. 3, pp. 303-312.
Refs: 46
ISSN: 0167-4889 CODEN: BAMRDP
PUBLISHER IDENT.: S 0167-4889(99)00142-1
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19991229
Last Updated on STN: 19991229

AB Previous data show a relation between GSH content and **proliferation** of normal and **tumour** cells. We recently demonstrated a specific involvement of GSH in the autophosphorylation activity of the platelet-derived growth factor (PDGF) receptor in NIH3T3 fibroblasts. In this study we demonstrate that the stimulation by PDGF of serum-starved NIH3T3 cells increases cellular GSH content, while no change in oxidized GSH content was measured. Experiments performed with actinomycin, cycloheximide and buthionine sulfoximide, a specific inhibitor of the rate-limiting enzyme of the de novo synthesis of GSH γ-glutamylcysteine synthetase (γ-GCS), confirm PDGF induction of GSH synthesis. These results provide the first demonstration that PDGF mediated transduction signals seem strictly related to mechanisms involved in the increase of γ-GCS activity associated with increased γ-GCS heavy subunit mRNA levels. In fact, serum and epidermal growth factor (EGF) stimulation of quiescent NIH3T3 and NIH3T3, which overexpress EGF receptor, does not affect GSH content or its synthesis. These data may be related to a possible GSH role in the **redox** regulation of cell **proliferation** mediated by PDGF.

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ACCESSION NUMBER: 1999396799 EMBASE
TITLE: **Redox** regulation of TNF signaling.
AUTHOR: Goossens V.; De Vos K.; Vercammen D.; Steemans M.; Vancompernolle K.; Fiers W.; Vandenabeele P.; Grooten J.
CORPORATE SOURCE: J. Grooten, Department of Molecular Biology, Flanders Interuniversity, Institute for Biotechnology, K.L. Ledeganckstraat 35, B-9000 Gent, Belgium
SOURCE: BioFactors, (**1999**) Vol. 10, No. 2-3, pp. 145-156.

Refs: 37
ISSN: 0951-6433 CODEN: BIFAEU
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19991202
Last Updated on STN: 19991202

AB TNF is produced during inflammation and induces, among other activities, cell death in sensitive **tumour** cells. We previously reported an increased generation of ROS in TNF-treated L929 fibrosarcoma cells prior to cell death. These ROS are of mitochondrial origin and participate in the cell death process. Presently, we focus on the identification of parameters that control ROS production and subsequent cytotoxicity. From the cytotoxic properties and susceptibility to scavenging of TNF-induced ROS as compared to pro-oxidant- induced ROS we conclude that TNF-mediated ROS generation and their lethal action are confined to the inner mitochondrial membrane. Oxidative substrates, electron-transport inhibitors, **glutathione** and **thiol**-reactive agents but also caspase inhibitors modulate TNF-induced ROS production and imply the existence of a negative regulator of ROS production. Inactivation of this regulator by a TNF-induced reduction of NAD(P)H levels and/or formation of intraprotein disulfides would be responsible for ROS generation.

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ACCESSION NUMBER: 1998215830 EMBASE
TITLE: Disruption of **redox** homeostasis in the transforming growth factor-α/c- myc transgenic mouse model of accelerated **hepatocarcinogenesis.**
AUTHOR: Factor V.M.; Kiss A.; Woitach J.T.; Wirth P.J.; Thorgeirsson S.S.
CORPORATE SOURCE: S.S. Thorgeirsson, National Cancer Institute, NIH, Bldg. 37, 37 Convent Drive MSC4255, Bethesda, MD 20892-4255, United States
SOURCE: Journal of Biological Chemistry, (**19 Jun 1998**) Vol. 273, No. 25, pp. 15846-15853.
Refs: 81
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980806
Last Updated on STN: 19980806

AB In previous studies we have demonstrated that transforming growth factor (TGF)-α/c-myc double transgenic mice exhibit an enhanced rate of cell **proliferation**, accumulate extensive DNA damage, and develop multiple liver **tumors** between 4 and 8 months of age. To clarify the biochemical events that may be responsible for the genotoxic and **carcinogenic** effects observed in this transgenic model, several parameters of **redox** homeostasis in the liver were examined prior to development of hepatic **tumors.** By 2 months of age, production of reactive oxygen species, determined by the peroxidation-sensitive fluorescent dye, 2',7'-dichlorofluorescin diacetate, was significantly elevated in TGF-α/c-myc transgenic hepatocytes versus either wild type or c-myc single transgenic cells, and occurred in

parallel with an increase in lipid peroxidation. Concomitantly with a rise in oxidant levels, antioxidant defenses were decreased, including total **glutathione** content and the activity of **glutathione** peroxidase, whereas **thioredoxin** reductase activity was not changed. However, hepatic **tumors** which developed in TGF- α/c-myc mice exhibited an increase in **thioredoxin** reductase activity and a very low activity of **glutathione** peroxidase. Furthermore, specific deletions were detected in mtDNA as early as 5 weeks of age in the transgenic mice. These data provide experimental evidence that co-expression of TGF-α and c- myc transgenes in mouse liver promotes overproduction of reactive oxygen species and thus creates an oxidative stress environment. This phenomenon may account for the massive DNA damage and acceleration of **hepatocarcinogenesis** observed in the TGF-α/c-myc mouse model.

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ACCESSION NUMBER: 1998215763 EMBASE
TITLE: Reversible inactivation of protein-tyrosine phosphatase 1B in A431 cells stimulated with epidermal growth factor.
AUTHOR: Lee S.-R.; Kwon K.-S.; Kim S.-R.; Rhee S.G.
CORPORATE SOURCE: S.G. Rhee, Bldg. 3, National Institutes of Health, Bethesda, MD 20892, United States. sgrhee@helix.nih.gov
SOURCE: Journal of Biological Chemistry, (**19 Jun 1998**) Vol. 273, No. 25, pp. 15366-15372.
Refs: 54
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980806
Last Updated on STN: 19980806

AB Stimulation of various cells with growth factors results in a transient increase in the intracellular concentration of H2O2 that is required for growth factor-induced protein tyrosine phosphorylation. The effect of H2O2 produced in response to epidermal growth factor (EGF) on the activity of protein-tyrosine phosphatase 1B (PTP1B) was investigated in A431 human epidermoid **carcinoma** cells. H2O2 inactivated recombinant PTP1B in vitro by oxidizing its catalytic site cysteine, most likely to sulfenic acid. The oxidized enzyme was reactivated more effectively by **thioredoxin** than by **glutaredoxin** or **glutathione** at their physiological concentrations. Oxidation by H2O2 prevented modification of the catalytic cysteine of PTP1B by iodoacetic acid, suggesting that it should be possible to monitor the oxidation state of PTP1B in cells by measuring the incorporation of radioactivity into the enzyme after lysis of the cells in the presence of radiolabeled iodoacetic acid. The amount of such radioactivity associated with PTP1B immunoprecipitated from A431 cells that had been stimulated with EGF for 10 min was 27% less than that associated with PTP1B from unstimulated cells. The amount of iodoacetic acid-derived radioactivity associated with PTP1B reached a minimum 10 min after stimulation of cells with EGF and returned to base line values by 40 min, suggesting that the oxidation of PTP1B is reversible in cells. These results indicate that the activation of a receptor tyrosine kinase by binding of the corresponding growth factor may not be sufficient to increase the steady state level of protein tyrosine phosphorylation in cells and that concurrent inhibition

of protein-tyrosine phosphatases by H2O2 might also be required.

L38 ANSWER 36 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1998182919 EMBASE
TITLE: Antioxidants reduce cyclooxygenase-2 expression, prostaglandin production, and **proliferation** in colorectal **cancer** cells.
AUTHOR: Chinery R.; Beauchamp R.D.; Shyr Y.; Kirkland S.C.; Coffey R.J.; Morrow J.D.
CORPORATE SOURCE: R.J. Coffey, G1 Cancer Program, CC-2218 Medical Center North, Vanderbilt University Medical Center, Nashville, TN 37232-2583, United States. coffeyrj@ctrvax.vanderbilt.edu
SOURCE: Cancer Research, (**1 Jun 1998**) Vol. 58, No. 11, pp. 2323-2327.
Refs: 23
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980727
Last Updated on STN: 19980727

AB Increased expression of cyclooxygenase (COX) and overproduction of prostaglandins (PGs) have been implicated in the development and progression of colorectal **cancer** (CRC). Recent observations suggest that reactive oxygen intermediates play a role in **tumor** cell growth regulation and expression of the inducible COX, COX-2. We therefore evaluated the effects of various antioxidants on COX expression and cellular growth in the human CRC cell line HCA-7. The antioxidants **pyrrolidinedithiocarbamate** (PDTC), **N-acetylcysteine**, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox), and U74006 decreased PG production, intracellular **redox** status, and cellular growth in a concentration-dependent manner. The decrease in cellular growth was associated with the induction of apoptosis. Unlike the selective COX inhibitors 1-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-5-[(4- fluoro)phenyl]pyrazole (SC 58125) and (2-cyclohexyloxy-4- nitrophenyl)methanesulfonamide (NS 398) that inhibit COX-2 catalytic activity, these antioxidants decreased COX-2 expression at the transcriptional level. Combined treatment of HCA-7 cells with PDTC and SC 58125 resulted in an additive decrease in PG levels and anchorage-dependent and -independent growth. Furthermore, whereas antioxidants or SC 58125 reduced **tumor** growth in vivo, coadministration of PDTC and SC 58125 resulted in actual **tumor** regression. These results suggest that combined therapy with NSAIDs and antioxidants might be useful in the prevention and/or treatment of CRC.

L38 ANSWER 37 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1998121794 EMBASE
TITLE: Mechanisms of inhibition of the **thioredoxin** growth factor system by **antitumor** 2-imidazolyl disulfides.
AUTHOR: Kirkpatrick D.L.; Kuperus M.; Dowdeswell M.; Potier N.; Donald L.J.; Kunkel M.; Berggren M.; Angulo M.; Powis G.
CORPORATE SOURCE: D.L. Kirkpatrick, Department of Chemistry, University of Regina, Regina, Sask. S4S 0A2, Canada.

kirkpaly@leroy.cc.uregina.ca
SOURCE: Biochemical Pharmacology, (**1 Apr 1998**) Vol. 55, No. 7, pp. 987-994.
Refs: 26
ISSN: 0006-2952 CODEN: BCPCA6
PUBLISHER IDENT.: S 0006-2952(97)00597-2
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980507
Last Updated on STN: 19980507

AB The interactions of a series of 2-imidazolyl disulfide **antitumor** compounds with the **thioredoxin** reductase (TR)/ **thioredoxin** (hTrx) **redox** system have been studied. Disulfides III-2 (n-butyl 2-mercaptoimidazolyl disulfide) and VI-2 (ethyl 2-mercaptoimidazolyl disulfide) were substrates for reduction by TR with K(m) values of 43 and 48 μM. Disulfides IV-2 (1-methylpropyl 2-mercaptoimidazolyl disulfide) and DLK-36 (benzyl 2-mercaptoimidazolyl disulfide) were competitive inhibitors of the reduction of hTrx by TR with K(i) values of 31 μM. None of the disulfides were substrates for reduction by human **glutathione** reductase. The disulfides caused reversible thioalkylation of hTrx at the **redox** catalytic site as shown by the fact that there was no thioalkylation of a mutant hTrx where both the catalytic site Cys32 and Cys35 residues were replaced by Ser. In addition, the disulfides caused a slower irreversible inactivation of hTrx as a substrate for reduction by TR, with half-lives for III-2 of 30 min, for IV-2 of 4 hr, and for IX-2 (t-butyl 2-mercaptoimidazolyl disulfide) of 24 hr. This irreversible inactivation of hTrx occurred at concentrations of the disulfides an order of magnitude below those that inhibited TR, and involved the Cys73 of hTrx, which is outside the conserved **redox** catalytic site, as shown by the resistance to inactivation of a mutant hTrx where Cys73 was replaced by Ser. Electrophoretic and mass spectral analyses of the products of the reaction between the disulfides and hTrx show that modification of 1-3 Cys residues of the protein occurred in a concentration-dependent fashion. The disulfides inhibited the hTrx dependent **proliferation** of MCF-7 breast **cancer** cells with IC50 values for III-2 and IV-2 of 0.2 and 1.2 μM, respectively. The results show that although the catalytic sites of TR and hTrx are reversibly inhibited by the 2-imidazolyl disulfides, it is the irreversible thioalkylation of Cys73 of hTrx by the disulfides chat most probably accounts for the inhibition of **thioredoxin** dependent cell growth by the disulfides.

L38 ANSWER 38 OF 67 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 1998138892 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9518260
TITLE: **Thiol redox** modulation of **tumor** necrosis factor-alpha responsiveness in cultured AIDS-related Kaposi's sarcoma cells.
AUTHOR: Mallery S R; Landwehr D J; Ness G M; Clark Y M; Hohl C M
CORPORATE SOURCE: Departments of Oral Surgery and Pathology, Colleges of Dentistry and Medicine, Ohio State University, Columbus 43210, USA.
CONTRACT NUMBER: CA UO1 66531 (NCI)

DE RO1 12183 (NIDCR)
R01 48547
SOURCE: Journal of cellular biochemistry, (1998 Mar 1) 68 (3) 339-54.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980407
Last Updated on STN: 20000303
Entered Medline: 19980325

AB Both clinical and experimental evidence indicates that AIDS-related Kaposi's sarcoma (AIDS-KS) has a multifactorial pathogenesis with factors such as HIV viral load, latent virus induction, and opportunistic infections contributing to disease progression. However, a consistent feature that unites these apparently diverse putative etiologic agents is sustained serum elevations of pro-inflammatory cytokines such as **tumor** necrosis factor-alpha (TNF-alpha). While virtually every cell responds to TNF-alpha with gene activation, the extent of TNF-alpha-mediated cellular signaling is regulated by a delicate balance between signal activation and signal arresting events. Reactive oxygen intermediates (ROI), which are generated as a consequence of TNF-alpha membrane interaction, are part of this TNF-alpha-initiated cellular activation cascade. Previous studies in our laboratory have shown that AIDS-KS cells possess impaired oxygen intermediate scavenging capacities, thereby establishing conditions permissive for the intracellular retention of ROI. In this study, we used cellular capacity to upregulate the cytoprotective enzyme superoxide dismutase (SOD) to address the extent of cellular response to TNF-alpha. Concurrent with the SOD analyses, nucleotide profiles were obtained to assess cellular bioenergetic responses during TNF-alpha challenge. **Proliferative** growth levels of mitochondrial (Mn)SOD activities showed an activity spectrum ranging from lowest activity in AIDS-KS cells, to intermediate levels in matched, nonlesional cells from the AIDS-KS donors, to highest activities in HIV normal fibroblasts. In contrast, following TNF-alpha challenge, the AIDS-KS and KS donor nonlesional cells showed a 11.89- and 5.86-fold respective increase in MnSOD activity, while the normal fibroblasts demonstrated a 1.35-fold decrease. Subsequent **thiol redox** modulation studies showed that only the normal fibroblast cultures showed a potentiation of TNF-alpha-mediated MnSOD upregulation following GSH depletion. In addition, provision of the GSH precursor, **N-acetylcysteine** during TNF-alpha challenge only diminished MnSOD activity and mitochondrial compartmentalization in the AIDS-KS cells, a finding that likely reflects the lower levels of reduced **thiols** in this cellular population. Our data, which show that a perturbation in their cellular **thiol redox** status accentuates AIDS-KS cellular responsiveness to TNF-alpha, suggest a biochemical rationale for the recognized TNF-alpha AIDS-KS clinical correlation.

L38 ANSWER 39 OF 67 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 1998049564 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9388242
TITLE: Regulatory role for a novel human **thioredoxin** peroxidase in NF-kappaB activation.
AUTHOR: Jin D Y; Chae H Z; Rhee S G; Jeang K T
CORPORATE SOURCE: Laboratory of Molecular Microbiology, NIAID, National

Institutes of Health, Bethesda, Maryland 20892, USA.
SOURCE: Journal of biological chemistry, (1997 Dec 5) 272 (49) 30952-61.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
OTHER SOURCE: GENBANK-U25182
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980122
Last Updated on STN: 20030204
Entered Medline: 19980108

AB Reduction-oxidation (**redox**) plays a critical role in NF-kappaB activation. Diverse stimuli appear to utilize reactive oxygen species (e.g. hydrogen peroxide) as common effectors for activating NF-kappaB. Antioxidants govern intracellular **redox** status, and many such molecules can reduce H2O2. However, functionally, it does appear that different antioxidants are variously selective for **redox** regulation of certain transcription factors such as NF-kappaB. For NF-kappaB, **thioredoxin** has been described to be a more potent antioxidant than either **glutathione** or **N-acetylcysteine. Thioredoxin** peroxidase is the immediate enzyme that links reduction of H2O2 to **thioredoxin.** Several putative human **thioredoxin** peroxidases have been identified using recursive sequence searches/alignments with yeast or prokaryotic enzymes. None has been characterized in detail for intracellular function(s). Here, we describe a new human **thioredoxin** peroxidase, antioxidant enzyme AOE372, identified by virtue of its protein-protein interaction with the product of a **proliferation** association gene, pag, which is also a **thiol**-specific antioxidant. In human cells, AOE372 defines a **redox** pathway that specifically regulates NF-kappaB activity via a modulation of IkappaB-alpha phosphorylation in the cytoplasm. We show that AOE372 activity is regulated through either homo- or heterodimerization with other **thiol** peroxidases, implicating subunit assortment as a mechanism for regulating antioxidant specificities. AOE372 function suggests **thioredoxin** peroxidase as an immediate regulator of H2O2-mediated activation of NF-kappaB.

L38 ANSWER 40 OF 67 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 97400545 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9252380
TITLE: Generation of angiostatin by reduction and proteolysis of plasmin. Catalysis by a plasmin reductase secreted by cultured cells.
AUTHOR: Stathakis P; Fitzgerald M; Matthias L J; Chesterman C N; Hogg P J
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, School of Pathology and Department of Haematology, Prince of Wales Hospital, University of New South Wales, Sydney NSW 2052, Australia.
SOURCE: Journal of biological chemistry, (1997 Aug 15) 272 (33) 20641-5.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 19970916
Entered Medline: 19970904

AB Extracellular manipulation of protein disulfide bonds has been implied in diverse biological processes, including penetration of viruses and endotoxin into cells and activation of certain cytokine receptors. We now demonstrate reduction of one or more disulfide bonds in the serine proteinase, plasmin, by a reductase secreted by Chinese hamster ovary or HT1080 cells. Reduction of plasmin disulfide bond(s) triggered proteolysis of the enzyme, generating fragments with the domain structure of the angiogenesis inhibitor, angiostatin. Two of the known reductases secreted by cultured cells are protein disulfide isomerase and **thioredoxin**, and incubation of plasmin with these purified reductases resulted in angiostatin fragments comparable with those generated from plasmin in cell culture. **Thioredoxin**-derived angiostatin inhibited **proliferation** of human dermal microvascular endothelial cells with half-maximal effect at approximately 0.2 microg/ml. Angiostatin made by cells and by purified reductases contained free sulfhydryl group(s), and S-carbamidomethylation of these **thiol** group(s) ablated biological activity. Neither protein disulfide isomerase nor **thioredoxin** were the reductases used by cultured cells, because immunodepletion of conditioned medium of these proteins did not affect angiostatin generating activity. The plasmin reductase secreted by HT1080 cells required a small cofactor for activity, and physiologically relevant concentrations of reduced **glutathione** fulfilled this role. These results have consequences for plasmin activity and angiogenesis, particularly in the context of **tumor** growth and metastasis. Moreover, this is the first demonstration of extracellular reduction of a protein disulfide bond, which has general implications for cell biology.

L38 ANSWER 41 OF 67 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 97240750 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9120263
TITLE: Adult T cell leukemia (ATL)-derived factor/human **thioredoxin** prevents apoptosis of lymphoid cells induced by L-cystine and **glutathione** depletion: possible involvement of **thiol**-mediated **redox** regulation in apoptosis caused by pro-oxidant state.
AUTHOR: Iwata S; Hori T; Sato N; Hirota K; Sasada T; Mitsui A; Hirakawa T; Yodoi J
CORPORATE SOURCE: Department of Biological Responses, Kyoto University, Japan.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1997 Apr 1) 158 (7) 3108-17.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 20000303
Entered Medline: 19970424

AB **Thiol** compounds, such as L-cysteine and **glutathione** (GSH), play crucial roles in the regulation of lymphocyte **proliferation.** In this study, we analyzed the effect of L-cystine

and GSH depletion on lymphocyte survival and investigated the regulatory roles of adult T cell leukemia (ATL)-derived factor (ADF)/human **thioredoxin** (hTRX) in relation to these low m.w. **thiols.** MT-1, MT-2, and Jurkat cells underwent apoptosis when cultured in the L-cystine- and GSH-free medium within 18 to 24 h. Dichlorofluorescin oxidation assay indicated that the apoptosis in MT-1 and MT-2 cells was preceded by an increase in the level of intracellular hydrogen peroxide (H2O2). The addition of catalase and recombinant ADF/hTRX (rADF) partially blocked the apoptosis in a dose-dependent manner. rADF has been also shown to enhance the internalization of L-cystine into MT-2 cells in a dose-dependent manner, whereas oxidized rADF or mutated rADF that has no insulin-reducing activity failed to do so. Furthermore, culture in the L-cystine- and GSH-free medium lowered the cellular GSH content of PHA blasts, which was restored dose-dependently by rADF. These data suggest that the inability to neutralize oxidative stress results in the apoptosis of lymphoid cells under L-cystine- and GSH-depleted conditions. The protective effects of rADF may be explained by direct scavenging action on H2O2 (catalase-like activity) or by indirect neutralizing effects on the pro-oxidant status through enhancing the L-cystine internalization and elevating the intracellular GSH content.

L38 ANSWER 42 OF 67 MEDLINE on STN
ACCESSION NUMBER: 97160620 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9006954
TITLE: Characterization of a secretory type Theileria parva **glutaredoxin** homologue identified by novel screening procedure.
AUTHOR: Ebel T; Middleton J F; Frisch A; Lipp J
CORPORATE SOURCE: Vienna International Research Cooperation Center, University of Vienna, A-1235 Vienna, Austria.
SOURCE: Journal of biological chemistry, (1997 Jan 31) 272 (5) 3042-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U48417
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19970321
Entered Medline: 19970313

AB The schizont stage of the protozoan parasite Theileria parva induces features characteristic of **tumor** cells in infected bovine T-cell lines. Most strikingly T. parva-infected cell lines acquire unlimited growth potential in vitro. Their **proliferative** state is entirely dependent on the presence of a viable parasite within the host cell cytoplasm. It has been postulated that parasite proteins either secreted into the host cell or expressed on the parasite surface membrane are involved in the parasite-host cell interaction. We used an in vitro transcription-translation-membrane translocation system to identify T. parva-derived cDNA clones encoding secretory or membrane proteins. Within 600 clones we found one encoding a 17-kDa protein which is processed by microsomal membranes to a 14-kDa protein (11E), presumably by signal peptidase. The processed form is expressed in the T-cell line TpM803 harboring viable parasites. By immunolocalization we show that the 11E protein mostly resides within the parasite, often in close vicinity to membranous structures, but in addition it appears at the surface membrane. Amino acid sequence comparison suggests that 11E belongs to the

**glutaredoxin** family, but is unique so far in containing a signal sequence for endoplasmic reticulum membrane translocation.

L38 ANSWER 43 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1998048667 EMBASE
TITLE: Luminal peroxides in intestinal **thiol**-disulfide balance and cell turnover.
AUTHOR: Tak Yee Aw
CORPORATE SOURCE: T.Y. Aw, Dept. of Molecular/Cellular Physiol, LSU Medical Center, Shreveport, LA, United States
SOURCE: Comparative Biochemistry and Physiology - B Biochemistry and Molecular Biology, (**1997**) Vol. 118, No. 3, pp. 479-485.
Refs: 65
ISSN: 0305-0491 CODEN: CBPBB8
PUBLISHER IDENT.: S 0305-0491(97)00220-4
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980227
Last Updated on STN: 19980227
AB Dietary intake of highly polyunsaturated fats represents a major source of lipid hydroperoxides in the intestinal lumen. Under conditions of high peroxide intake, excessive concentrations of lipid hydroperoxides can persist in the gut lumen and contribute to impairment of mucosal GSH-dependent detoxication pathways, enterocyte dysfunction independent of cell injury, and development of gut pathologies, including **cancer** . This paper summarizes our current knowledge of the determinants of intestinal lipid hydroperoxide metabolism and of the physiological and biochemical processes in lipid peroxide-mediated changes in intestinal **redox** status, regulation of mucosal **thiol** and antioxidant balance and control of intestinal cell turnover. This discussion is pertinent to understanding dietary peroxides and **thiol redox** balance in intestinal physiology and pathophysiology and the potential benefit of oral GSH in preserving metabolic integrity of the intestinal epithelium.

L38 ANSWER 44 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 97137031 EMBASE
DOCUMENT NUMBER: 1997137031
TITLE: **Redox** state changes in density-dependent regulation of **proliferation.**
AUTHOR: Hutter D.E.; Till B.G.; Greene J.J.
CORPORATE SOURCE: J.J. Greene, Department of Biology, Catholic University of America, Washington, DC 20064, United States
SOURCE: Experimental Cell Research, (**1997**) Vol. 232, No. 2, pp. 435-438.
Refs: 25
ISSN: 0014-4827 CODEN: ECREAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 970527
Last Updated on STN: 970527

AB The ability of certain transcription factors to bind to DNA has been demonstrated to be influenced by the **redox** environment. Therefore, fluctuations in the **redox** state of the cell may regulate the transcription of genes which control **proliferation.** To assess whether changes in the **redox** state may be related to **proliferation**, levels of oxidized (GSSG) and reduced (GSH) **glutathione**, the primary modulators of the **redox** state, were measured in cultures of varying densities of normal human fibroblasts which exhibit contact inhibition of **proliferation**, as well as fibrosarcoma cells, which lack this mechanism of growth control. **Redox** potentials calculated from normal, **proliferating** fibroblasts were found to be -34 mV more reducing than confluent, contact-inhibited cells. However, fibrosarcoma cells did not demonstrate this modulation in **redox** state. Further, to delineate whether these **redox** changes were the consequence or the cause of contact inhibition, cultures of subconfluent **proliferating** fibroblasts were treated with modulators of **glutathione** synthesis. **Buthionine sulfoximine**, an inhibitor of GSH synthesis, induced a less reducing **redox** state and decreased **proliferation.** In contrast, GSH synthesis precursors caused a more reduced **redox** state and increased **proliferation.** Collectively, these results suggest an interrelationship between **redox** state and growth control.

L38 ANSWER 45 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 97259007 EMBASE
DOCUMENT NUMBER: 1997259007
TITLE: Nitric oxide and superoxide induced p53 and Bax accumulation during mesangial cell apoptosis.
AUTHOR: Sandau K.; Pfeilschifter J.; Brune B.
CORPORATE SOURCE: Dr. B. Brune, University of Erlangen-Numberg, Faculty of Medicine, Loschgestrasse 8, 91054 Erlangen, Germany
SOURCE: Kidney International, (**1997**) Vol. 52, No. 2, pp. 378-386.
Refs: 51
ISSN: 0085-2538 CODEN: KDYIA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 970918
Last Updated on STN: 970918

AB During **proliferative** glomerulonephritis, the early phase of mesangiolysis is linked to increased nitric oxide (NO·) production. NO· as well as superoxide (O2-) are inflammatory mediators that are generated by mesangial cells (MC) after cytokine stimulation. Added individually, both radicals induce MC apoptosis. However, the co-existence of a defined NO·/O2- ratio is cross-protective. Apoptosis is characterized by specific features such as chromatin condensation, DNA strand breaks, and the occurrence of apoptotic regulating proteins. The **tumor** suppressor p53 and Bax (Bcl-2 associated protein x) are considered to be classical death promotors,

which accumulate after toxic insults. To study p53 and Bax protein accumulation in NO· and/or O2- induced apoptosis, we used the NO-donor S- **nitrosoglutathione** (GSNO) and the **redox** cycler 2,3-dimethoxy-1,4-naphtoquione (DMNQ). Both agonists initiated DNA fragmentation in a concentration dependent manner associated with transient p53 and Bax up-regulation. Co- generation of NO·/O2- resulted not only in reduced DNA fragmentation, but also in decreased Bax accumulation. Comparable to the NO·/O2-co- generation, cytokines failed to induce apoptosis. In contrast, cytokines in combination with pyrrolidine **dithiocarbamate**, which blocks endogenous superoxide dismutase, allowed p53 and Bax accumulation as well as DNA fragmentation. Our results demonstrate p53 and Bax as early components in NO· and O2- induced rat MC apoptosis and point to the NO·/O2- interaction as a naturally occurring cell defense mechanism.

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ACCESSION NUMBER: 97260943 EMBASE
DOCUMENT NUMBER: 1997260943
TITLE: **Redox** control as a target for **anticancer** drug development.
AUTHOR: Kirkpatrick D.L.
CORPORATE SOURCE: D.L. Kirkpatrick, Department of Chemistry, University of Rgina, Regina, Sask. S4S 0A2, Canada
SOURCE: Current Pharmaceutical Design, (**1997**) Vol. 3, No. 3, pp. 305-322.
Refs: 302
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 970911
Last Updated on STN: 970911

AB Cells maintain an intracellular environment that is reducing in the face of all oxidizing extracellular environment. Regulated alterations in the intracellular **redox** state (**redox** signalling) can modulate events such as DNA synthesis, enzyme activation, selective gene expression and regulation of the cell cycle. The primary consequence of intracellular **redox** signalling is a change in the oxidation state of cysteine residues of key proteins. This review will examine a number of the cellular **redox** systems which are in place to control the **redox** state, including such proteins as **glutathione** and **glutathione** reductase. **thioredoxin** and **thioredoxin** reductase, the highly cysteine rich, metalothioneins and the Ref-1' protein which plays a role in the activity of AP-1 and NF-κB. Signalling processcs will be identified which are dependent on the **redox** state of controlling proteins and are potential targets for drug development and include transcription factors whose activation is a prerequisite for growth faster stimulated growth. The development of drugs which exploit the cellular **redox** state has grown dramatically over the last few years as the understanding of cellular **redox** has burgeoned. This review will attempt to present the current state of knowledge of agents in this category including those which exploit the hypoxic cellular environment,

those which participate through antioxidant pathways and the evolving area of interest involving agents which alter the signalling process through protein thioalkylation.

L38 ANSWER 47 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 97243511 EMBASE
DOCUMENT NUMBER: 1997243511
TITLE: Chemical-induced changes in intracellular **redox** state and in apoptosis.
AUTHOR: Jajte J.M.
CORPORATE SOURCE: Dr. J.M. Jajte, Department of Physical Hazards, Nofer Institute of Occupational Med., P.O. Box 199, 90-950 Lodz, Poland
SOURCE: International Journal of Occupational Medicine and Environmental Health, (**1997**) Vol. 10, No. 2, pp. 203-212.
Refs: 44
ISSN: 1232-1087 CODEN: IOMHEZ
COUNTRY: Poland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 970829
Last Updated on STN: 970829
AB Necrosis and apoptosis are two ways by which cells die. A major concept of apoptosis is that it is a controlled process. From this concept it follows that cells contain a molecule or molecules which under specific, regulated circumstances mediate cell death. Recent data confirm that oxygen free radicals can be mediators of apoptosis. Chemicals could induce apoptosis due to reactive oxygen species production and changes in the intracellular **redox** state. Therefore, a complete understanding of the processes involved in apoptosis, and mechanisms of its manipulation, could provide novel strategies to the control of xenobiotic toxicity and give an impetus to design new therapeutic interventions.

L38 ANSWER 48 OF 67 JICST-EPlus COPYRIGHT 2005 JST on STN
ACCESSION NUMBER: 970501427 JICST-EPlus
TITLE: Retinoid induces growth inhibition of adult T-cell leukemia cells.
AUTHOR: MIYATAKE J; MAEDA Y
CORPORATE SOURCE: Kinki Univ. School of Medicine, Osaka, JPN
SOURCE: Acta Med Kinki Univ, (1997) vol. 22, no. 1, pp. 111-121.
Journal Code: S0990A (Fig. 9, Tbl. 1, Ref. 32)
ISSN: 0386-6092
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
STATUS: New
AB The effects of retinoic acid (RA) on the cell growth and expression of interleukin-2 (IL-2) receptor (IL-2RA/p55, Tac, CD25) by the human T lymphotropic virus type I positive (HTLV-I( + )) T cell lines, HUT102 and ATL-2, were investigated. Incubation of these cells with RA resulted in marked growth inhibition and down-regulation of CD25 expression. Four clones of HUT102 cell lines were established by limiting dilution, and RA was shown to inhibit the growth and CD25 expression in three of these

clones, but in the fourth. However, RA did not induce growth inhibition of the HTLV-I-negative T cell lines, MOLT-4 and Jurkat, and of normal lymphocytes that had been stimulated wih phytohemagglutinin. We hydothesized that the sensivity to retinoids depends on an imbalance in intracellular **redox** potential. To examine the effect of exogenous **thiol** compounds for the growth inhibition of HTLV-I( + ) T cell lines induced by RA, these cell lines were cultured with serveral **thiol** compounds (ATL-derived factor, thioredoxin, L-cystine and **glutathione** (GSH)), following the addition of RA in **thiolfree** medium. Unexpectedly, **thiol** compounds alone, when added after RA, did not restore the growth inhibition of HTLV-I( + ) T cell lines induced by RA. However, when those cells were preincubated with **thiol** compounds for 24 hrs, no RA-induced growth inhibition was observed. These findings suggest that intracellular reductive environments induced by **thiol** compounds are associated with resistance to RA of HTLV-I( + ) T cells, and that **thiol** compounds may play an important role in HTLV-I( + ) T cell **proliferation.** (author abst.)

L38 ANSWER 49 OF 67 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 97112983 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8943236
TITLE: Induction of p21 mediated by reactive oxygen species formed during the metabolism of aziridinylbenzoquinones by HCT116 cells.
AUTHOR: Qiu X; Forman H J; Schonthal A H; Cadenas E
CORPORATE SOURCE: Department of Molecular Pharmacology and Toxicology, School of Pharmacy, University of Southern California, Los Angeles, California 90033, USA.
CONTRACT NUMBER: 1RO1 ES05423 (NIEHS)
SOURCE: Journal of biological chemistry, (1996 Dec 13) 271 (50) 31915-21.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970117

AB Aziridinylbenzoquinones are a group of **antitumor** agents that elicit cytotoxicity by generating either alkylating intermediates or reactive oxygen species. The mechanism of toxicity may not always, however, involve profound damage of cellular constituents, but may involve a cytostatic effect through interference with the cell cycle. In this context, we have examined the induction of the cell cycle inhibitor p21 (WAF1, CIP1, or sdi1), whose overexpression suppresses the growth of various **tumor** cells, in human **tumor** cells metabolizing 3,6-diaziridinyl-1,4-benzoquinone (DZQ) and its C2,C5-substituted derivatives: 2,5-bis-(carboethoxyamino) (AZQ) and 2, 5-bis-2(-hydroxyethylamino) (BZQ). Both DZQ and AZQ were effectively activated by HCT116 human colonic **carcinoma** cells; the activation of the former involved largely a dicoumarol-sensitive activity, whereas that of the latter appeared to be accomplished primarily by one-electron transfer reductases. BZQ was not a substrate for the dicoumarol-sensitive enzyme in HCT116 cells. Cellular activation of the first two quinones was associated with formation of oxygen-centered radicals as detected by EPR in conjunction with the spin trap 5,5'-dimethyl-1-pyrroline-N-oxide. The

**redox** transitions of DZQ involved hydroxyl radical formation and were strongly inhibited by catalase, whereas those of AZQ showed a strong superoxide anion component sensitive to superoxide dismutase. These signals were suppressed by **N-acetylcysteine** with concomitant production of a thiyl radical adduct. This suggests an effective electron transfer between the **thiol** and free radicals formed during the activation of these quinones. DZQ and AZQ induced significantly the expression of p21 in HCT116 cells, but a 10-fold higher concentration of AZQ was required to achieve the level of induction elicited by DZQ. BZQ had little effect on p21 expression. p21 induction at both mRNA and protein levels correlated with the inhibition of either cyclin-dependent kinase activity or cell **proliferation.** p21 induction elicited by the above quinones was inhibited by **N-acetylcysteine**, whereas the non-sulfur analog, N-acetylalanine, was without effect. Catalase and superoxide dismutase did not effect p21 induction by aziridinylbenzoquinones in HCT116 cells, thus suggesting that extracellular sources of oxygen radicals generated by plasma membrane reductases have no influence in the expression of this gene. Hydrogen peroxide, a product of quinone **redox** cycling, elicited an increase of p21 mRNA levels in HCT116 and K562 human chronic myelogenous leukemia cells. The latter lacks p53, one of the activators of p21 transcription, thus suggesting that p21 expression can be accomplished in a p53-independent manner in these cells. This study suggests that p21 induction is mediated by an increase in the cellular steady-state concentration of oxygen radicals and that the greater effectiveness in p21 induction by DZQ may be related to its efficient metabolism by NAD(P)H:quinone oxidoreductase activity in HCT116 cells.

L38 ANSWER 50 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96303120 EMBASE
DOCUMENT NUMBER: 1996303120
TITLE: Selenite and selenate inhibit human lymphocyte growth via different mechanisms.
AUTHOR: Spyrou G.; Bjornstedt M.; Skog S.; Holmgren A.
CORPORATE SOURCE: Department of Bioscience, Center for Biotechnology, Karolinska Institutet,S-141 57 Huddinge, Sweden
SOURCE: Cancer Research, (**1996**) Vol. 56, No. 19, pp. 4407-4412.
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 961021
Last Updated on STN: 961021

AB Selenium compounds like selenite and selenate have strung inhibitory effects, particularly on mammalian **tumor** cell growth by unknown mechanisms. We found that the addition of sodium selenite and sodium selenate inhibited the growth of human 3B6 and BL41 lymphocytes. Selenite was more potent because 10 μM selenite produced a growth inhibitory effect similar to that of 250 μM selenate. The mechanism of action of selenite and selenate appears to be different. 3B6 and BL41 cells treated with selenite accumulated in the S-phase; however, selenate caused an accumulation of cells in G2. Selenite- mediated growth inhibition was irreversible, although the effects of selenate could be reversed.

Selenite, in contrast to selenate, is efficiently reduced by the **thioredoxin** system (**thioredoxin**, **thioredoxin** reductase, and NADPH). At concentrations required to observe a similar effect on cell growth, the activity of **thioredoxin** reductase, recently shown to be a selenoprotein, increased in selenite-treated cells and decreased in selenate-treated cells. Ribonucleotide reductase activity was inhibited in an in vitro assay by selenite and **selenodiglutathione** but not by selenate. These results show that selenite and selenate use different mechanisms to inhibit cell growth.

L38 ANSWER 51 OF 67 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 97139536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8986137
TITLE: Oxidative inactivation of **thioredoxin** as a cellular growth factor and protection by a Cys73-->Ser mutation.
AUTHOR: Gasdaska J R; Kirkpatrick D L; Montfort W; Kuperus M; Hill S R; Berggren M; Powis G
CORPORATE SOURCE: Arizona Cancer Center, University of Arizona Health Services Center, Tucson 85724-5024, USA.
CONTRACT NUMBER: CA48725 (NCI)
SOURCE: Biochemical pharmacology, (1996 Dec 13) 52 (11) 1741-7. Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970123

AB **Thioredoxin** (Trx) is a widely distributed **redox** protein that regulates several intracellular **redox**-dependent processes and stimulates the **proliferation** of both normal and **tumor** cells. We have found that when stored in the absence of reducing agents, human recombinant Trx undergoes spontaneous oxidation, losing its ability to stimulate cell growth, but is still a substrate for NADPH-dependent reduction by human **thioredoxin** reductase. There is a slower spontaneous conversion of Trx to a homodimer that is not a substrate for reduction by **thioredoxin** reductase and that does not stimulate cell **proliferation.** Both conversions can be induced by chemical oxidants and are reversible by treatment with the **thiol** reducing agent **dithiothreitol.** SDS-PAGE suggests that Trx undergoes oxidation to monomeric form(s) preceding dimer formation. We have recently shown by X-ray crystallography that Trx forms a dimer that is stabilized by an intermolecular Cys73-Cys73 disulfide bond. A Cys73-->Ser mutant Trx (C73S) was prepared to determine the role of Cys73 in oxidative stability and growth stimulation. C73S was as effective as Trx in stimulating cell growth and was a comparable substrate for **thioredoxin** reductase. C73S did not show spontaneous or oxidant-induced loss of activity and did not form a dimer. The results suggest that Trx can exist in monomeric forms, some of which are mediated by Cys73 that do not stimulate cell **proliferation** but can be reduced by **thioredoxin** reductase. Cys73 is also involved in formation of an enzymatically inactive homodimer, which occurs on long term storage or by chemical oxidation. Thus, although clearly involved in protein inactivation, Cys73 is not necessary for the growth stimulating activity of Trx.

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ACCESSION NUMBER: 96311210 EMBASE
DOCUMENT NUMBER: 1996311210
TITLE: Nitric oxide donors suppress erythropoietin production in vitro.
AUTHOR: Schobersberger W.; Hoffmann G.; Fandrey J.
CORPORATE SOURCE: Physiologisches Institut I, Universitat Bonn, Nussallee 11,D-53115 Bonn, Germany
SOURCE: Pflugers Archiv European Journal of Physiology, (**1996**) Vol. 432, No. 6, pp. 980-985.
ISSN: 0031-6768 CODEN: PFLABK
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 961106
Last Updated on STN: 961106

AB Many inflammatory diseases are associated with a **hypoproliferative** anaemia. Patients with this anaemia often present with serum erythropoietin (EPO) concentrations that are too low for the degree of their anaemia. Proinflammatory cytokines, in addition to their inhibitory effects on **proliferation** of erythroid progenitors, could contribute to the pathogenesis of this anaemia by reducing EPO production. Because several cytokines stimulate nitric oxide (NO) synthase we propose that nitric oxide might mediate the suppression of EPO production during inflammation. In order to test this hypothesis we investigated the effects of NO donors on 24-h hypoxia-induced EPO production in the hepatocellular **carcinoma** cell line HepG2. Following application of the NO donors sodium nitroprusside (SNP), 3-morpholinosydnonimine (SIN-1), and S-nitroso-N-acetyl-D, L-penicillamine (SNAP), EPO production was dose-dependently reduced: compared to the untreated control EPO production was lowered by 89% with SNP (1000 μM), by 66% with SIN-1 (1000 μM), and by 72% with SNAP (500 μM). In contrast, 8-bromo-cGMP did not inhibit EPO formation. Since pyrogallol (300 μM) and H2O2 (250 μM) showed a comparable suppression of EPO synthesis, we propose that NO might affect EPO production either by a similar direct influence on the cellular **redox** state or via increasing the cellular content of reactive oxygen species.

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ACCESSION NUMBER: 96019392 EMBASE
DOCUMENT NUMBER: 1996019392
TITLE: The organization of the human GSTP1-1 gene promoter and its response to retinoic acid and cellular **redox** status.
AUTHOR: Xia C.; Hu J.; Ketterer B.; Taylor J.B.
CORPORATE SOURCE: Department of Molecular Pathology, University College London, Windeyer Building, Cleveland Street,London W1P 6DB, United Kingdom
SOURCE: Biochemical Journal, (**1996**) Vol. 313, No. 1, pp. 155-161.
ISSN: 0264-6021 CODEN: BIJOAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 960130
Last Updated on STN: 960130

AB High levels of expression of GSTP1-1 are associated with cell **proliferation**, embryogenesis and malignancy. Given the role of **glutathione** S-transferase (GST) in detoxication, it is possible that GSTP1-1 evolved specifically to protect **proliferating** cells and share regulatory mechanisms with other cellular genes which are involved in cell division and **tumorigenesis.** We have previously shown that the expression of GSTP1 is suppressed by retinoic acid (RA) in the presence of the retinoic acid receptor (RAR) as a result of decreased transcription from its promoter. Through deletion analysis, we show here that the RA-RAR-dependent repression is mediated by the region -73 to +8. Further mutation analysis of this region indicates that the DNA sequence required for RA-RAR-dependent repression co-localizes with a consensus activator protein-1 (AP1) site essential for the promoter activity. The degree of repression correlates with the residual activity of the AP1 site. There are two adjacent G/C boxes. The one immediately downstream from the AP1 site is not essential for the promoter activity, but mutation of the second, further downstream, impairs the promoter. On the other hand, mutation of either of these two G/C boxes has little effect on RA-RAR suppression. We also show that the expression of GSTP1 is regulated by the **redox** status of the cell. Using the chloramphenicol acetyltransferase assay system, we have demonstrated that treatment with H2O2 induced transcription from the promoter and that this effect can be blocked by pre-incubation with **N-acetylcysteine** (NAG). It was shown that the induction by H2O2, is mediated by trans-acting factor NF-κB (nuclear factor κB), via a putative NF-κB site,'GGGACCCTCC', located from -96 to -86. Co-transfection with an NF-κB expression construct increased the promoter activity, an effect which could be blocked by co-transfection with an IκB (MAD-3) expression construct. Deletion of the NF-κB site abolished the effect of both H2O2, and co-transfection of NF-κB. Interestingly, **NAC** is also an inducer for GSTP1. The effect of **NAC** was shown to be mediated largely by the AP1 site, since mutation of this site abolished the induction by NAG.

L38 ANSWER 54 OF 67 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 96291625 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8726363
TITLE: Reduction-oxidation (**redox**) state regulation of extracellular matrix metalloproteinases and tissue inhibitors in cardiac normal and transformed fibroblast cells.
AUTHOR: Tyagi S C; Kumar S; Borders S
CORPORATE SOURCE: Department of Medicine, Dalton Cardiovascular Research Center, University of Missouri-Columbia 65212, USA.
CONTRACT NUMBER: GM-48595 (NIGMS)
SOURCE: Journal of cellular biochemistry, (1996 Apr) 61 (1) 139-51. Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961025

Last Updated on STN: 20021218
Entered Medline: 19961015

AB Latent matrix metalloproteinases (MMPs) in normal myocardium are activated in end-stage heart failure. In vitro oxidized **glutathione** (GSSG) activates myocardial MMPs which contains a cysteine residue. In vivo GSSG induce the collagen lysis and cardiac dilatation. To assess whether **thiol** and non-**thiol** reducing agents have direct effect on the interstitial human heart fibroblast (HHF) **proliferation** and MMP expression, HHF and polyoma virus transformed fibroblast cells were cultured with or without the **thiol**-containing reduced (GSH) or oxidized (GSSG) **glutathiones**, pyrrolidine **dithiocarbamate** (PDTC) and **N-acetylcysteine** (**NAC**), and non-**thiol** ascorbic acid. After 100 micrograms/ml (approximately 0.3 mM) GSH or PDTC treatment the **proliferative** (synthetic) phenotype of transformed fibroblast cells was changed to quiescent (contractile) phenotype. Also, after GSH, PDTC, and ascorbic acid treatment the medium was then analyzed for MMP activity by zymography. The results indicate reduction in MMP expression in transformed fibroblast cells after GSH and PDTC treatments and no effect after ascorbic acid treatment. Based on reverse zymography, we observed the level of tissue inhibitor of metalloproteinase (TIMP) at a decreased level in transformed cells. The effect of the reducing agent at the gene transcription was measured by estimating mRNA (Northern blot analysis) of MMP and of TIMP in the cells that were cultured in medium in the presence and absence of GSH. These results indicate that GSH induces MMP-2 and MMP-1 expression in normal HHF and that GSH reduces MMP-2 and MMP-1 in transformed fibroblast cells. After the treatment, the TIMP-2 level was repressed in normal HHF and TIMP-2 level increased in transformed fibroblast cells. These events are dependent on the nuclear transcription factor activity on the collagenase promoter in normal HHF cells. On the other hand, in polyoma transform fibroblast cells these events are not dependent on this collagenase promoter. These results suggest that oxidative environment induces normal HHF cell **proliferation**, and the reducing agent decreases normal HHF cell **proliferation** by inducing MMP and repressing TIMP gene transcription. In transformed cells reducing agents inhibit MMP expression and increase TIMP levels, which suggests a role of antioxidants in preventing **tumorigenesis.**

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ACCESSION NUMBER: 96295578 EMBASE
DOCUMENT NUMBER: 1996295578
TITLE: Cytoprotective agents for anthracyclines.
AUTHOR: Dorr R.T.
CORPORATE SOURCE: Arizona Cancer Center, 1515 N Campbell Ave,Tucson, AZ 58724, United States
SOURCE: Seminars in Oncology, (**1996**) Vol. 23, No. 4 SUPPL. 8, pp. 23-34.
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 961021
Last Updated on STN: 961021

AB Anthracycline-induced cardiotoxicity is believed to be related to the generation of reactive oxygen species by at least two mechanisms: enzymatic reduction of the quinone with subsequent **redox** cycling and/or formation of an iron-anthracycline complex capable of intramolecular reduction and **redox** cycling. Both pathways may lead to the production of superoxide anions and highly reactive metabolites, such as hydroxyl radicals and hydrogen peroxide. As a result, membrane lipid peroxidation may ensue, producing damage in tissues like the heart, which have low antioxidant defenses (superoxide dismutase **glutathione** and especially, **glutathione**-peroxidase). Pharmacologic methods of interrupting this cycle have involved numerous antioxidants, such as the sulfhydryls **N-acetylcysteine** and **cysteamine**, and the lipophilic vitamin alpha tocopherol. Unfortunately, none of these compounds has been proven to be cardioprotective in patients receiving doxorubitin. In contrast, the water-soluble d-isomer of the iron chelator razoxane, dexrazoxane or ICRF-187, has been shown to reduce doxorubicin-induced cardiomyopathy. This has afforded greater cumulative doses of doxorubicin to be safely administered. The cytoprotective effect is apparently limited to the heart since there is no effect on **antitumor** efficacy and, unfortunately, no reduction in gastrointestinal toxicity, and with a slight increase in myelosuppression. More recent preclinical studies have also demonstrated cardioprotective activity for the **aminothiol** amifostine (WR-2721). In vitro, this agent has been shown to scavenge superoxide anions and hydroxyl radicals, the latter effect mediated by the active (dephosphorylated) metabolite, WR-1065. In **tumor**-bearing mice, amifostine reduces the lethality of high doses of doxorubicin without affecting **antitumor** activity. Finally, in vitro studies in neonatal rat heart cells have shown direct evidence of anthracycline cardioprotection for both amifostine and WR-1065. Cytoprotective drug levels of either agent were limited to 2.0 μg/mL, which is one tenth of the achievable peak plasma levels in humans. At this concentration, a 15-minute sulfhydryl pretreatment significantly prevented doxorubicin-induced depressions of myocyte adenosine triphosphate levels. Overall, these studies suggest that amifostine may have cytoprotective activity against doxorubicin-induced cardiac damage. Animal studies in a chronically dosed doxorubicin model are indicated; if positive, clinical trials testing this hypothesis will be warranted.

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ACCESSION NUMBER: 95077360 EMBASE
DOCUMENT NUMBER: 1995077360
TITLE: Superoxide and hydrogen peroxide in relation to mammalian cell **proliferation.**
AUTHOR: Burdon R.H.
CORPORATE SOURCE: Department Bioscience/Biotechnology, University of Strathclyde,Glasgow G4 0NR, United Kingdom
SOURCE: Free Radical Biology and Medicine, (**1995**) Vol. 18, No. 4, pp. 775-794.
ISSN: 0891-5849 CODEN: FRBMEH
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 950405
Last Updated on STN: 950405

AB A wide variety of normal and malignant cell types generate and release

superoxide or hydrogen peroxide in vitro either in response to specific cytokine/growth factor stimulus or constitutively in the case of **tumour** cells. These species at submicromolar levels appear to act as novel intra and intercellular 'messengers' capable of promoting growth responses in culture. The mechanisms may involve direct interaction with specific receptors or oxidation of growth signal transduction molecules such as protein kinases, protein phosphatases, transcription factors, or transcription factor inhibitors. It is also possible that hydrogen peroxide may modulate the **redox** state and activity of these important signal transduction proteins indirectly through changes in cellular levels of GSH and GSSG. Critical balances appear to exist in relation to cell **proliferation** on one hand and lipid peroxidation and cell death on the other. Progression to a more prooxidant state whilst initially leading to enhanced **proliferative** responses results subsequently in increased cell death.

L38 ANSWER 57 OF 67 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 95136249 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7834639
TITLE: High rates of **thioredoxin** secretion correlate with growth arrest in hepatoma cells.
AUTHOR: Rubartelli A; Bonifaci N; Sitia R
CORPORATE SOURCE: Laboratory of Clinical Pathology, National Institute for Cancer Research, Genova, Italy.
SOURCE: Cancer research, (1995 Feb 1) 55 (3) 675-80. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950314
Last Updated on STN: 19970203
Entered Medline: 19950228

AB **Thioredoxin** (TRX), a disulfide-reducing intracellular **dithiol** enzyme, is synthesized by both normal liver cells and the **hepatocarcinoma** cell line HepG2. Only the former, however, secrete abundant TRX extracellularly. When cultured in mild reducing conditions, HepG2 cells but not normal hepatocytes increase the rate of TRX secretion and undergo growth inhibition accompanied by morphological changes. Also, recombinant TRX inhibits **proliferation** of HepG2 cells. In contrast, exogenous **thiols** and TRX stimulate **proliferation** of a B-cell lymphoma line, indicating that different cell types respond differently to variations in the extracellular **redox** potential.

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ACCESSION NUMBER: 95189904 EMBASE
DOCUMENT NUMBER: 1995189904
TITLE: Increased levels of oxidized **glutathione** in CD4+ lymphocytes associated with disturbed intracellular **redox** balance in human immunodeficiency virus type 1 infection.
AUTHOR: Aukrust P.; Svardal A.M.; Muller F.; Lunden B.; Berge R.K.; Ueland P.M.; Froland S.S.
CORPORATE SOURCE: Clinical Immunol./Infect. Dis. Sec., Medical Department A, Rikshospitalet,N-0027 Oslo, Norway

SOURCE: Blood, (**1995**) Vol. 86, No. 1, pp. 258-267.
ISSN: 0006-4971 CODEN: BLOOAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 950712
Last Updated on STN: 950712

AB We investigated the intracellular **glutathione redox** status in isolated lymphocyte subpopulations and monocytes in patients with human immunodeficiency virus type 1 (HIV-1) infection and in healthy controls. CD4+ lymphocytes from HIV-1-infected patients were primarily characterized by a substantial increase in oxidized **glutathione** levels and a considerable decrease in the ratio of reduced to total **glutathione**, in most cases below 0.5 in patients with symptomatic HIV-1 infection, rather than decreased levels of reduced **glutathione.** The increase in oxidized **glutathione** was strongly correlated with low numbers of CD4+ lymphocytes in peripheral blood and impaired stimulated interleukin-2 production and **proliferation** in peripheral blood mononuclear cells, which is compatible with an immunopathogenic role for these **redox** disturbances. The HIV-1-infected patients with the most advanced clinical and immunologic disease were also characterized by an increase in levels of reduced **glutathione** in monocytes, suggesting that the **glutathione redox** cycle may be differentially regulated in CD4+ lymphocytes and monocytes. We could not confirm previous reports suggesting cysteine deficiency as a major cause of disturbed **glutathione** homeostasis during HIV-1 infection. The demonstrated **glutathione** abnormalities were correlated with raised serum levels of **tumor** necrosis factor α. These findings suggest that a therapeutical approach, which can restore the **glutathione redox** dysbalance in CD4+ lymphocytes and decrease the inflammatory stress, may be worthwhile exploring in HIV-1 infection.

L38 ANSWER 59 OF 67 EMBASE 
on STN
ACCESSION NUMBER: 95081084 EMBASE
DOCUMENT NUMBER: 1995081084
TITLE: Analysis of studies related to **tumorigenicity** induced by hydroquinone.
AUTHOR: Whysner J.; Verna L.; English J.C.; Williams G.M.
CORPORATE SOURCE: Environmental Health/Safety Program, Division of Pathology/Toxicology, American Health Foundation,Valhalla, NY 10595, United States
SOURCE: Regulatory Toxicology and Pharmacology, (**1995**) Vol. 21, No. 1, pp. 158-176.
ISSN: 0273-2300 CODEN: RTOPDW
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
025 Hematology
028 Urology and Nephrology
035 Occupational Health and Industrial Medicine
046 Environmental Health and Pollution Control
048 Gastroenterology
052 Toxicology
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 950412
Last Updated on STN: 950412

AB Hydroquinone (HQ) produced renal adenomas in male F344 rats, and these **tumors** appeared to arise from areas of spontaneous progressive nephropathy; the nephropathy itself has been found to be enhanced by HQ. Other **neoplasms** were not confirmed to be causally related to HQ among the reported bioassays. In the male F344 rat, HQ administered alone was not DNA reactive. HQ produced enhanced **proliferation** of renal tubular epithelium, presumably through toxicity involving **glutathione** conjugate formation. In the kidney, bone marrow, and other tissues, HQ may induce toxicity by **redox** cycling and lipid peroxidation. In bone marrow, HQ may produce microtubulin dysfunction, which is a plausible explanation for positive cytogenetic tests, the only consistently positive genotoxicity effect reported for HQ. Although HQ is a metabolic product of benzene, several lines of evidence suggest that the effects of HQ exposure are significantly different from those of benzene. Based upon the plausible mechanisms by which HQ may produce kidney **tumors** in male rats, we have concluded that occupational exposure levels of HQ are not predicted to be a **cancer** risk for humans.

L38 ANSWER 60 OF 67 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 94267168 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8207197
TITLE: **Thiol**-mediated **redox** regulation of lymphocyte **proliferation.** Possible involvement of adult T cell leukemia-derived factor and **glutathione** in transferrin receptor expression.
AUTHOR: Iwata S; Hori T; Sato N; Ueda-Taniguchi Y; Yamabe T; Nakamura H; Masutani H; Yodoi J
CORPORATE SOURCE: Department of Biological Responses, Kyoto University, Japan.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1994 Jun 15) 152 (12) 5633-42.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940721
Last Updated on STN: 20000303
Entered Medline: 19940713

AB The **proliferative** response of PBMC to PHA, Con A, OKT3 mAb and IL-2-dependent **proliferation** of PHA-blasts was examined in a **thiol**-free environment (cultured in a L-cystine- and GSH-free medium). [3H]TdR incorporation assay and cell cycle analysis revealed that stimulated PBMC could not enter the S phase when deprived of these **thiol** compounds. In **thiol**-free cultures, an increase in intracellular free Ca2+ concentration and IL-2R alpha-chain/p 55 (Tac) induction was still observed, whereas transferrin receptor induction was markedly reduced, suggesting that the **proliferative** response of mitogenically stimulated PBMC was arrested in the late G1 phase in which transferrin receptor is induced. In GSH-depleted cultures, a similar reduction of the **proliferative** response of PBMC and PHA-blasts was observed when the concentration of L-cystine was lowered, in a dose-dependent manner. Each reduction or loss of **proliferative** response was partially restored by supplementation of 2-ME or adult T cell leukemia-derived factor (ADF)/human **thioredoxin** which is

considered to be an endogenous **dithiol**-reducing factor. L-Cystine transport analysis showed that mitogenically stimulated PBMC and PHA blasts incorporated L-cystine, whereas resting PBMC did not. Furthermore, ADF as well as 2-ME exhibited an enhancing activity on the L-cystine transport in PHA blasts. Together with the fact that L-cystine transport is a limiting step in **glutathione** synthesis, these findings suggest that GSH and ADF might cooperate in the **thiol**-mediated **redox** regulation process and might also play key roles in cell cycle (late G1 to S) progression of activated lymphocytes.

L38 ANSWER 61 OF 67 EMBASE  on STN

ACCESSION NUMBER: 94142819 EMBASE
DOCUMENT NUMBER: 1994142819
TITLE: **Redox** regulation of signal transduction: Tyrosine phosphorylation and calcium influx.
AUTHOR: Staal F.J.T.; Anderson M.T.; Staal G.E.J.; Herzenberg L.A.; Gitler C.; Herzenberg L.A.
CORPORATE SOURCE: Department of Genetics, Stanford Univ. School of Medicine,Stanford, CA 94305, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (**1994**) Vol. 91, No. 9, pp. 3619-3622.
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 940602
Last Updated on STN: 940602

AB Studies presented here show that altering the intracellular **redox** balance by decreasing **glutathione** levels profoundly affects early signal transduction events in human T cells. In a T-cell receptor (TCR) signaling model, short- term pretreatment with **buthionine sulfoximine**, which specifically decreases intracellular **glutathione**, essentially abrogates the stimulation of calcium influx by anti-CD3 antibodies without significantly impairing other aspects of TCR-initiated signal transduction, such as overall levels of TCR- stimulated tyrosine phosphorylation. In an inflammatory-cytokine signaling model, the failure of **tumor** necrosis factor α to stimulate more than minimal tyrosine phosphorylation in lymphocytes is overcome by **buthionine sulfoximine** pretreatment-i.e., **tumor** necrosis factor α stimulates extensive tyrosine phosphorylation in **glutathione**-depleted lymphocytes. These **redox**-dependent changes in T-cell responsiveness suggest that the **glutathione** deficiency that we and others have demonstrated in human immunodeficiency virus-infected individuals may contribute significantly to the immunodeficiency and the increased inflammatory reactions in these individuals.

L38 ANSWER 62 OF 67 MEDLINE on STN DUPLICATE 25
ACCESSION NUMBER: 95019213 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7933622
TITLE: Measurement of ADF/**thioredoxin** in human serum and its clinical significance.
AUTHOR: Kitaoka Y; Sachi Y; Mori T; Yodoi J
CORPORATE SOURCE: Department of Biological Responses, Kyoto University.

SOURCE: Rinsho byori. Japanese journal of clinical pathology, (1994 Aug) 42 (8) 853-9.
Journal code: 2984781R. ISSN: 0047-1860.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19941222
Entered Medline: 19941104

AB The adult T cell leukemia (ATL)-derived factor (ADF) was first described as an interleukin 2 receptor alpha chain (IL-2R alpha) inducing factor which is produced by an HTLV-I infected cell line. Subsequent purification and gene cloning proved that it is a human homologue of a bacterial reducing coenzyme, **thioredoxin** (TRX). ADF/human TRX (hTRX) has multiple functions both in the extracellular and intracellular compartments, such as cytokine activity, **dithiol**-reducing activity and radical scavenging activity. ADF/hTRX can facilitate the interactions between the transcriptional factors and its target DNA sequences, which may result in the overexpression of IL -2R alpha in HTLV-I infected cells. Recently, we have detected the presence of ADF/hTRX in human serum (sADF) obtained from healthy volunteers using the insulin reducing assay and Western blotting analysis. Another endogenous **redox** regulator, **glutathione** (GSH) system, has long been studied for its relation to cell **proliferation** and activation. Our recent data showed that **thiol** compounds such as L-cysteine and GSH may be involved in the activation and cell cycle progression of stimulated lymphocytes. We have also found that ADF/hTRX promotes L-cysteine transport into the cells and increases intracellular GSH content, indicating the close association between ADF/hTRX and GSH systems. **Redox** regulation by ADF/hTRX and GSH systems seems to play an important role in regulating cell **proliferation** and activation. To assess the possible alteration of the sADF level in pathological conditions, such as viral infections, an ELISA system for ADF/hTRX was recently established using two different monoclonal antibodies against rADF.(ABSTRACT TRUNCATED AT 250 WORDS)

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ACCESSION NUMBER: 94220957 EMBASE
DOCUMENT NUMBER: 1994220957
TITLE: **Redox** reagents and staurosporine inhibit stimulation of the transcription regulator NF-κB following **tumour** necrosis factor treatment of chronic B-leukaemia cells.
AUTHOR: Jabbar S.A.B.; Hoffbrand A.V.; Wickremasinghe R.G.
CORPORATE SOURCE: Department of Haematology, Royal Free Hospital School Medicine, Pond Street,London NW3 2QG, United Kingdom
SOURCE: Leukemia Research, (**1994**) Vol. 18, No. 7, pp. 523-530.
ISSN: 0145-2126 CODEN: LEREDD
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 940803
Last Updated on STN: 940803

AB B-chronic lymphocytic leukaemia (B-CLL) and hairy cell leukaemia cells (HCL) are refractory to stimulation by several cytokines which activate normal B-cells. However, **tumour** necrosis factor (TNF) promotes the **proliferation** of these cells. TNF regulates some of its cellular responses via the transcription factor NF-κB. Using an electrophoretic mobility shift assay, we demonstrate that TNF treatment of B-CLL and HCL cells in vitro resulted in the augmentation of NF-κB levels. In haemopoietic cell lines, TNF induction of NF-κB is mediated via the generation of reactive oxygen intermediates and by the activation of protein kinase C (PKC). We have used activators and inhibitors of these pathways to unravel TNF signalling in the cells of ten patients with B-CLL and two with HCL, using the increase in NF-κB levels following TNF treatment as an end point. Raising **glutathione** levels with N-acetyl cysteine substantially reduced NF-κB induction by TNF in two of four samples, as did treatment of cells with the antioxidant butylated-hydroxytoluene in all three samples tested. These data suggest that **redox** mechanisms are involved in TNF signalling in these cells. Treatment with the PKC activator phorbol myristate acetate failed to activate NF-κB suggesting that this enzyme does not mediate the induction of NF-κB in these cells. However, the protein kinase inhibitor staurosporine inhibited TNF induction of NF-κB in four of five samples, suggesting that staurosporine-sensitive protein kinases (other than PKC) are involved in the signalling pathway. Our results suggest that PKC-independent pathways, including pathways sensitive to **redox** reagents, mediate the induction of NF-κB by TNF in chronic B-leukaemia cells. Additionally, these data suggest that defects in PKC-mediated pathways may contribute to the general reluctance of B-CLL and HCL cells to respond to mitogenic signals.

L38 ANSWER 64 OF 67 MEDLINE on STN DUPLICATE 26
ACCESSION NUMBER: 94132729 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7507967
TITLE: Inhibition of activation-induced death in T cell hybridomas by **thiol** antioxidants: oxidative stress as a mediator of apoptosis.
AUTHOR: Sandstrom P A; Mannie M D; Buttke T M
CORPORATE SOURCE: Department of Microbiology and Immunology, East Carolina University, School of Medicine, Greenville, NC 27858.
SOURCE: Journal of leukocyte biology, (1994 Feb) 55 (2) 221-6.
Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940318
Last Updated on STN: 19970203
Entered Medline: 19940308

AB **N-Acetylcysteine** (**NAC**) is a well established **thiol** antioxidant which, after uptake, deacylation and conversion to **glutathione** functions as both a **redox** buffer and a reactive oxygen intermediate scavenger. We report here that **NAC** completely blocks activation induced death and associated DNA fragmentation of myelin basic protein (MBP) specific T cell hybridomas. Conversely, **NAC** had very little effect on the antigen driven **proliferation** of a MBP specific T cell line similar to that from

which the hybridomas were derived. **NAC** displayed an analogous absolute inhibition of mitogen mediated activation induced death, even if added up to 3 h post activation. Although **glutathione** was as efficient as **NAC** at blocking activation induced death, **dithiothreitol** displayed minimal inhibition while L-cysteine had no effect at all. The observation that certain **thiol** antioxidants such as **NAC** and **glutathione** can completely block the activation induced death of T cell hybridomas implicates **redox** regulation in this process.

L38 ANSWER 65 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 94169017 EMBASE
DOCUMENT NUMBER: 1994169017
TITLE: Oxidative damage and repair in the developing nervous system.
AUTHOR: Verity M.A.
CORPORATE SOURCE: Division of Neuropathology, Brain Research Institute, UCLA Center for the Health Sciences,Los Angeles, CA 90024-1732, United States
SOURCE: NeuroToxicology, (**1994**) Vol. 15, No. 1, pp. 81-92.
ISSN: 0161-813X CODEN: NRTXDN
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 940629
Last Updated on STN: 940629

AB Excessive production of reactive oxygen species (ROS) is a recognized cause of cell injury. In contrast to such well recognized cell injury, oxidative stress plays a role in cell **proliferation**, differentiation and **tumor** promotion. This review examines the role of oxidative stress in initiating and promoting the establishment of normal or abnormal neuronal patterns and subsequent neurogenesis within the central and peripheral nervous system. In particular, the role of apoptosis in both normal and abnormal neuronal development and maturation will be examined with especial reference to the induction of apoptotic cell death following abusive ligand- induced ion movements. The interaction of oxidant stress and immediate-early response gene activation is discussed with further reference to the induction of apoptosis. While glutamate receptor activation appears mandatory for coordinate maturation and neuritogenesis, such neuronal survival and differentiation is intimately dependent upon the intracellular **glutathione** **redox** potential, maintained by cystine uptake. Selected examples of reactive oxygen species induced injury pertaining to developmental neurotoxicology are presented and include starvation, irradiation injury and glutamate excitotoxicity.

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ACCESSION NUMBER: 91203269 EMBASE
DOCUMENT NUMBER: 1991203269
TITLE: Augmented anti-**proliferative** effect in combined use of human lymphotoxin with a nitrosourea derivative, ACNU, and the involvement of **glutathione** **redox** cycle.
AUTHOR: Mashiba H.; Matsunaga K.; Kakutani T.

CORPORATE SOURCE: Division of Immunology, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 815, Japan
SOURCE: International Journal of Immunopharmacology, (**1991**) Vol. 13, No. 4, pp. 333-338.
ISSN: 0192-0561 CODEN: IJIMDS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 911216
Last Updated on STN: 911216

AB The cytotoxic or cytostatic effect of the combined use of human lymphotoxin (LT) with 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosour ea hydrochloride (ACNU) on cells or Meth A **tumor** cells was studied. Simultaneous addition of LT derived from a human lymphoid cell line with ACNU (200 or 500 μg/ml) significantly augmented the cytotoxic effect. Similar augmented inhibition was obtained when LT was added to ACNU-treated L cells. The pre-treatment of Meth A **tumor** cells with ACNU (25 or 50 μg/ml) augmented recombinant human LT-mediated cytostasis. However, the addition of **glutathione** (1.0 mg/ml) to ACNU-treated Meth A **tumor** cells significantly nullified the augmented **antiproliferative** effect of LT (10 U/ml). These results suggest that augmentation of the anti-**proliferative** effect on **tumor** cells could be induced through the combined use of LT with ACNU by lowering the intracellular level of **glutathione.**

L38 ANSWER 67 OF 67 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 88144244 EMBASE
DOCUMENT NUMBER: 1988144244
TITLE: Toxic effects of acute **glutathione** depletion by **buthionine sulfoximine** and dimethylfumarate on murine mammary **carcinoma** cells.
AUTHOR: Dethlefsen L.A.; Lehman C.M.; Biaglow J.E.; Peck V.M.
CORPORATE SOURCE: Department of Radiology, Section of Experimental Oncology, University of Utah Health Sciences Center, Salt Lake City, UT 84132, United States
SOURCE: Radiation Research, (**1988**) Vol. 114, No. 2, pp. 215-224.
ISSN: 0033-7587 CODEN: RAREAE
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 911211
Last Updated on STN: 911211

AB **Glutathione** (GSH) depletion to .simeq. 5% of control for 48 h or longer by 0.05 mM L-**buthionine sulfoximine** (BSO) led to appreciable toxicity for the 66 murine mammary **carcinoma** cells growing in vitro [L.A. Dethlefsen et al., Int. J. Radiat. Oncol.

Biol. Phys. 12, 1157-1160 (1986)]. Such toxicity in normal, **proliferating** cells in vivo would be undesirable. Thus the toxic effects after acute GSH depletion to .simeq. 5% of control by BSO plus dimethylfumarate (DMF) were evaluated in these same 66 cells to determine if this anti-**proliferative** effect could be minimized. Two hours of 0.025 mM DMF reduced GSH to 45% of control, while 6 h of 0.05 mM BSO reduced it to 16%. However, BSO (6 h) plus DMF (2 h) and BSO (24 h) plus DMF (2 h) reduced GSH to 4 and 2%, respectively. The incorporation (15-min pulses) of radioactive precursors into protein and RNA were unaffected by these treatment protocols. In contrast, cell growth was only modestly affected, but the incorporation of [3H]thymidine into DNA was reduced to 64% of control by the BSO (24 h) plus DMF (2 h) protocol even though it was unaffected by the BSO (6 h) plus DMF (2 h) treatment. The cellular plating efficiencies from both protocols were reduced to .simeq. 75% of control cells. However, the aerobic radiation response, as measured by cell survival, was not modified at doses of either 4.0 or 8.0 Gy. The growth rates of treated cultures, after drug removal, quickly returned to control rates and the resynthesis of GSH in cells from both protocols was also rapid. The GSH levels after either protocol were slightly above control by 12 h after drug removal, dramatically over control (.simeq. 200%) by 24 h, and back to normal by 48 h. Thus even a relatively short treatment with BSO and DMF resulting in a GSH depletion to 2-5% of control had a marked effect on DNA synthesis and plating efficiency and a modest effect on cellular growth. One cannot rule out a direct effect of the drugs, but presumably the **antiproliferative** effects are due to a depletion of nuclear GSH with the subsequent inhibition of the GSH/**glutaredoxin**-mediated conversion of ribonucleotides to deoxyribonucleotides. However, even after extended treatment, upon drug removal, GSH was rapidly resynthesized and cellular DNA synthesis and growth quickly resumed.

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L35           85 SEA FILE=HCAPLUS ABB=ON  L31 OR L34
L39          808 SEA FILE=USPATFULL ABB=ON  L35 AND (PRD<19990216 OR PD<19990216
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L41          140 SEA FILE=USPATFULL ABB=ON  L40 AND ?CHEMOTHERAPEUTIC?(W)?AGENT?
L42            8 SEA FILE=USPATFULL ABB=ON  L41 AND NON?(W)?VIRAL?

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L42  ANSWER 1 OF 8  USPATFULL on STN
ACCESSION NUMBER:        2004:184092  USPATFULL
TITLE:                   Nucleic acid and corresponding protein entitled 98P4B6
                         useful in treatment and detection of cancer
INVENTOR(S):             Raitano, Arthur B., Los Angeles, CA, UNITED STATES
                         Ge, Wangmao, Culver City, CA, UNITED STATES
                         Jakobovits, Aya, Beverly Hills, CA, UNITED STATES
                         Challita-Eid, Pia M., Encino, CA, UNITED STATES
                         Faris, Mary, Los Angeles, CA, UNITED STATES

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2004141975      A1   20040722
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APPLICATION INFO.: US 2003-407484 A1 20030404 (10)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-455486, filed on 6 Dec 1999, PENDING Continuation-in-part of Ser. No. US 1999-323873, filed on 1 Jun 1999, GRANTED, Pat. No. US 6329503

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 1998-91183P | 19980630 (60) | <-- |
| | US 1998-87520P | 19980601 (60) | <-- |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kate H. Murashige, Morrison & Foerster LLP, Suite 500, 3811 Valley Centre Drive, San Diego, CA, 92130
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 97 Drawing Page(s)
LINE COUNT: 22646
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel gene 098P4B6 (also designated STEAP-2) and its encoded protein, and variants thereof, are described wherein 98P4B6 exhibits tissue specific expression in normal adult tissue, and is aberrantly expressed in the **cancers** listed in Table I. Consequently, 98P4B6 provides a diagnostic, prognostic, prophylactic and/or therapeutic target for **cancer.** The 98P4B6 gene or fragment thereof, or its encoded protein, or variants thereof, or a fragment thereof, can be used to elicit a humoral or cellular immune response; antibodies or T cells reactive with 98P4B6 can be used in active or passive immunization.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L42 ANSWER 2 OF 8 USPATFULL on STN
ACCESSION NUMBER: 2003:294798 USPATFULL
TITLE: Manipulating nitrosative stress to kill pathologic microbes, pathologic helminths and pathologically **proliferating** cells or to upregulate nitrosative stress defenses
INVENTOR(S): Stamler, Jonathan S., Chapel Hill, NC, UNITED STATES
Griffith, Owen W., Milwaukee, WI, UNITED STATES

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2003207815 | A1 | 20031106 |
| APPLICATION INFO.: | US 2003-417238 | A1 | 20030417 (10) |

RELATED APPLN. INFO.: Division of Ser. No. US 2001-13455, filed on 13 Dec 2001, GRANTED, Pat. No. US 6608110 Continuation of Ser. No. US 2000-690989, filed on 18 Oct 2000, GRANTED, Pat. No. US 6359004 Division of Ser. No. US 1999-361167, filed on 27 Jul 1999, GRANTED, Pat. No. US 6180824 Division of Ser. No. US 1997-852490, filed on 7 May 1997, GRANTED, Pat. No. US 6057367

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 1996-25819P | 19960830 (60) | <-- |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Eric S. Spector, JONES, TULLAR & COOPER, P.C., Eads Station, P.O. Box 2266, Arlington, VA, 22202

NUMBER OF CLAIMS: 69
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 3394
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Mammals are treated for infections or for conditions associated with pathologically **proliferating** mammalian cell growth (for example certain **cancers**, restenosis, benign prostatic hypertrophy) by administration of a manipulator of nitrosative stress to selectively kill or reduce the growth of the microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically **proliferating** mammalian cells. Novel agents include α-alkyl-S-alkyl-homocysteine sulfoximines wherein the α-alkyl contains 2 to 8 carbon atoms, and the S-alkyl-contains 1 to 10 carbon atoms. In another invention herein, mammals in need of increased nitrosative stress defenses are treated, e.g., humans at risk for a stroke because of having had a transient ischemic attack, are treated. Treatments to increase nitrosative stress defenses include, for example, repeated administrations of low doses of manipulators of nitrosative stress so that the subject treated has increased tolerance to nitrosative stress. In still another invention, mammals are treated for protozoal infections by systemic administration of L-buthionine-S-sulfoximine and agent that increases nitrosative stress.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L42 ANSWER 3 OF 8 USPATFULL on STN
ACCESSION NUMBER: 2003:258639 USPATFULL
TITLE: 207 human secreted proteins
INVENTOR(S): Ni, Jian, Germantown, MD, UNITED STATES
Ebner, Reinhard, Gaithersburg, MD, UNITED STATES
LaFleur, David W., Washington, DC, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Olsen, Henrik S., Gaithersburg, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES
Shi, Yanggu, Gaithersburg, MD, UNITED STATES
Florence, Kimberly A., Rockville, MD, UNITED STATES
Wei, Ying-Fei, Berkeley, CA, UNITED STATES
Florence, Charles, Rockville, MD, UNITED STATES
Hu, Jing-Shan, Mountain View, CA, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Kyaw, Hla, Frederick, MD, UNITED STATES
Fischer, Carrie L., Burke, VA, UNITED STATES
Ferrie, Ann M., Painted Post, NY, UNITED STATES
Fan, Ping, Potomac, MD, UNITED STATES
Feng, Ping, Gaithersburg, MD, UNITED STATES
Endress, Gregory A., Florence, MA, UNITED STATES
Dillon, Patrick J., Carlsbad, CA, UNITED STATES
Carter, Kenneth C., North Potomac, MD, UNITED STATES
Brewer, Laurie A., St. Paul, MN, UNITED STATES
Yu, Guo-Liang, Berkeley, CA, UNITED STATES
Zeng, Zhizhen, Lansdale, PA, UNITED STATES
Greene, John M., Gaithersburg, MD, UNITED STATES

| NUMBER | KIND | DATE |
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PATENT INFORMATION: US 2003181692 A1 20030925
APPLICATION INFO.: US 2001-933767 A1 20010822 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2001-US5614, filed on 21 Feb 2001, PENDING Continuation-in-part of Ser. No. US 1998-205258, filed on 4 Dec 1998, PENDING

| | NUMBER | DATE | |
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| PRIORITY INFORMATION: | US 2000-184836P | 20000224 (60) | |
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| | US 1997-49375P | 19970606 (60) | <-- |
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| | US 1997-57645P | 19970905 (60) | |
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| | US 1997-57769P | 19970905 (60) | |
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| US 1997-57647P | 19970905 | (60) |
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| US 1997-57662P | 19970905 | (60) |
| US 1997-57646P | 19970905 | (60) |
| US 1997-57654P | 19970905 | (60) |
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| US 1997-57644P | 19970905 | (60) |
| US 1997-57765P | 19970905 | (60) |
| US 1997-57762P | 19970905 | (60) |
| US 1997-57775P | 19970905 | (60) |
| US 1997-57648P | 19970905 | (60) |
| US 1997-57774P | 19970905 | (60) |
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| US 1997-57770P | 19970905 | (60) |
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| US 1997-57761P | 19970905 | (60) |
| US 1997-57760P | 19970905 | (60) |
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| US 1997-57778P | 19970905 | (60) |
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| US 1997-57628P | 19970905 | (60) |
| US 1997-57777P | 19970905 | (60) |
| US 1997-57634P | 19970905 | (60) |
| US 1997-70923P | 19971218 | (60) |
| US 1998-92921P | 19980715 | (60) |
| US 1998-94657P | 19980730 | (60) |
| US 1997-70923P | 19971218 | (60) |
| US 1998-92921P | 19980715 | (60) |
| US 1998-94657P | 19980730 | (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 32746
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L42 ANSWER 4 OF 8 USPATFULL on STN
ACCESSION NUMBER: 2003:141028 USPATFULL
TITLE: MANIPULATING NITROSATIVE STRESS TO KILL PATHOLOGIC MICROBES, PATHOLOGIC HELMINTHS AND PATHOLOGICALLY **PROLIFERATING** CELLS OR TO UPREGULATE NITROSATIVE STRESS DEFENSES
INVENTOR(S): Stamler, Jonathan S., Chapel Hill, NC, UNITED STATES
Griffith, Owen W., Milwaukee, WI, UNITED STATES

| NUMBER | KIND | DATE |
|---|---|---|

PATENT INFORMATION: US 2003096870 A1 20030522
US 6608110 B2 20030819
APPLICATION INFO.: US 2001-13455 A1 20011213 (10)
RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-690989, filed on 18 Oct 2000, GRANTED, Pat. No. US 6359004 Division of Ser. No. US 1999-361167, filed on 27 Jul 1999, GRANTED, Pat. No. US 6180824 Division of Ser. No. US 1997-852490, filed on 7 May 1997, GRANTED, Pat. No. US 6057367

| | NUMBER | DATE |
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| PRIORITY INFORMATION: | US 1996-25819P | 19960830 (60) <-- |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Eric S. Spector, JONES, TULLAR & COOPER, P.C., Eads Station, P.O. Box 2266, Arlington, VA, 22202
NUMBER OF CLAIMS: 69
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 3394
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Mammals are treated for infections or for conditions associated with pathologically **proliferating** mammalian cell growth (for example, certain **cancers**, restenosis, benign prostatic hypertrophy) by administration of a manipulator of nitrosative stress to selectively kill or reduce the growth of the microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically **proliferating** mammalian cells. Novel agents include α-alkyl-S-alkyl-homocysteine sulfoximines wherein the α-alkyl contains 2 to 8 carbon atoms, and the S-alkyl- contains 1 to 10 carbon atoms. In another invention herein, mammals in need of increased nitrosative stress defenses are treated, e.g., humans at risk for a stroke because of having had a transient ischemic attack, are treated. Treatments to increase nitrosative stress defenses include, for example, repeated administrations of low doses of manipulators of nitrosative stress so that the subject treated has increased tolerance to nitrosative stress. In still another invention, mammals are treated for protozoal infections by systemic administration of L-buthionine-S-sulfoximine and agent that increases nitrosative stress.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L42 ANSWER 5 OF 8 USPATFULL on STN
ACCESSION NUMBER: 2002:57833 USPATFULL
TITLE: Manipulating nitrosative stress to upregulate nitrosative stress defenses
INVENTOR(S): Stamler, Jonathan S., Chapel Hill, NC, United States
Griffith, Owen W., Milwaukee, WI, United States
PATENT ASSIGNEE(S): Duke University, Durham, NC, United States (U.S. corporation)
The Medical College of Wisconsin, Milwaukee, WI, United States (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6359004 | B1 | 20020319 |
| APPLICATION INFO.: | US 2000-690989 | | 20001018 (9) |

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-361167, filed on 27 Jul 1999, now patented, Pat. No. US 6180824 Division of

Ser. No. US 1997-852490, filed on 7 May 1997, now patented, Pat. No. US 6057367

| | NUMBER | DATE | |
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| PRIORITY INFORMATION: | US 1996-25819P | 19960830 (60) | <-- |

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Weddington, Kevin E.
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 3105
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Mammals are treated for infections or for conditions associated with pathologically **proliferating** mammalian cell growth (for example, certain **cancers**, restenosis, benign prostatic hypertrophy) by administration of a manipulator of nitrosative stress to selectively kill or reduce the growth of the microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically **proliferating** mammalian cells. Novel agents include α-alkyl-S-alkyl-homocysteine sulfoximines wherein the α-alkyl contains 2 to 8 carbon atoms, and the S-alkyl- contains 1 to 10 carbon atoms. In another invention herein, mammals in need of increased nitrosative stress defenses are treated, e.g., humans at risk for a stroke because of having had a transient ischemic attack, are treated. Treatments to increase nitrosative stress defenses include, for example, repeated administrations of low doses of manipulators of nitrosative stress so that the subject treated has increased tolerance to nitrosative stress. In still another invention, mammals are treated for protozoal infections by systemic administration of L-buthionine-S-sulfoximine and agent that increases nitrosative stress.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L42 ANSWER 6 OF 8 USPATFULL on STN
ACCESSION NUMBER: 2001:14679 USPATFULL
TITLE: Manipulating nitrosative stress to kill pathologic microbes, pathologic helminths and pathologically, **proliferating** cells or to upregulate nitrosative stress defenses
INVENTOR(S): Stamler, Jonathan S., Chapel Hill, NC, United States
Griffith, Owen W., Milwaukee, WI, United States
PATENT ASSIGNEE(S): Duke University, Durham, NC, United States (U.S. corporation)
The Medical College of Wisconsin, Milwaukee, WI, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 6180824 | B1 | 20010130 | |
| APPLICATION INFO.: | US 1999-361167 | | 19990727 (9) | |
| RELATED APPLN. INFO.: | Division of Ser. No. US 1997-852490, filed on 7 May 1997, now patented, Pat. No. US 6057367 | | | |

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 1996-25819P | 19960830 (60) | <-- |

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted
PRIMARY EXAMINER: Weddington, Kevin E.
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 3128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Mammals are treated for infection or for conditions associated with pathologically **proliferating** mammalian cell growth (for example, certain **cancers**, restenosis, benign prostatic hypertrophy) by administration of a manipulator of nitrosative stress to selectively kill or reduce the growth of the microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically **proliferating** mammalian cells. Novel agents include α-alkyl-S-alkyl-homocysteine sulfoximines wherein the α-alkyl contains 2 to 8 carbon atoms, and the S-alkyl- contains 1 to 10 carbon atoms. In another invention herein, mammals in need of increased nitrosative stress defenses are treated, e.g., humans at risk for a stroke because of having had a transient ischemic attack, are treated. Treatments to increase nitrosative stress defenses include, for example, repeated administrations of low doses of manipulators of nitrosative stress so that the subject treated has increased tolerance to nitrosative stress. In still another invention, mammals are treated for protozoal infections by systemic administration of L-buthionine-S-sulfoximine and agent that increases nitrosative stress.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L42 ANSWER 7 OF 8 USPATFULL on STN
ACCESSION NUMBER: 2000:54150 USPATFULL
TITLE: Manipulating nitrosative stress to kill pathologic microbes, pathologic helminths and pathologically **proliferating** cells or to upregulate nitrosative stress defenses
INVENTOR(S): Stamler, Jonathan S., Chapel Hill, NC, United States
Griffith, Owen W., Milwaukee, WI, United States
PATENT ASSIGNEE(S): Duke University, Durham, NC, United States (U.S. corporation)
The Medical College of Wisconsin Research Foundation, Inc., Milwaukee, WI, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 6057367 | | 20000502 | |
| APPLICATION INFO.: | US 1997-852490 | | 19970507 | (8) |

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 1996-25819P | 19960830 (60) | <-- |

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Weddington, Kevin E.
NUMBER OF CLAIMS: 66
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 3415
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Mammals are treated for infections or for conditions associated with pathologically **proliferating** mammalian cell growth (for

example, certain **cancers**, restenosis, benign prostatic hypertrophy) by administration of a manipulator of nitrosative stress to selectively kill or reduce the growth of the microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically **proliferating** mammalian cells. Novel agents include α-alkyl-S-alkyl-homocysteine sulfoximines wherein the α-alkyl contains 2 to 8 carbon atoms, and the S-alkyl-contains 1 to 10 carbon atoms. In another invention herein, mammals in need of increased nitrosative stress defenses are treated, e.g., humans at risk for a stroke because of having had a transient ischemic attack, are treated. Treatments to increase nitrosative stress defenses include, for example, repeated administrations of low doses of manipulators of nitrosative stress so that the subject treated has increased tolerance to nitrosative stress. In still another invention, mammals are treated for protozoal infections by systemic administration of L-buthionine-S-sulfoximine and agent that increases nitrosative stress.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L42 ANSWER 8 OF 8 USPATFULL on STN

| | |
|---|---|
| ACCESSION NUMBER: | 1998:156914 USPATFULL |
| TITLE: | Compounds and methods for the diagnosis, treatment and prevention of diseases of cell death |
| INVENTOR(S): | Brown, Robert, Needham, MA, United States<br>Horvitz, H. Robert, Cambridge, MA, United States<br>Rosen, Daniel R., Dedham, MA, United States |
| PATENT ASSIGNEE(S): | The General Hospital Corporation, Boston, MA, United States (U.S. corporation)<br>Massachusetts Institute of Technology, Cambridge, MA, United States (U.S. corporation) |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5849290 | | 19981215 | <-- |
| APPLICATION INFO.: | US 1995-486953 | | 19950607 (8) | |
| RELATED APPLN. INFO.: | Division of Ser. No. US 1994-204052, filed on 28 Feb 1994 which is a continuation-in-part of Ser. No. US 1993-23980, filed on 26 Feb 1993 | | | |
| DOCUMENT TYPE: | Utility | | | |
| FILE SEGMENT: | Granted | | | |
| PRIMARY EXAMINER: | Grimes, Eric | | | |
| LEGAL REPRESENTATIVE: | Clark & Elbing LLP | | | |
| NUMBER OF CLAIMS: | 6 | | | |
| EXEMPLARY CLAIM: | 1 | | | |
| NUMBER OF DRAWINGS: | 30 Drawing Figure(s); 17 Drawing Page(s) | | | |
| LINE COUNT: | 2365 | | | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is the family of genes responsible for the neurodegenerative diseases, particularly Amyotrophic Lateral Sclerosis. Methods and compounds for the diagnosis, prevention, and therapy of the disease are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d his ful

     (FILE 'HOME' ENTERED AT 16:52:53 ON 17 SEP 2005)

     FILE 'REGISTRY' ENTERED AT 16:56:53 ON 17 SEP 2005
L1             1 SEA ABB=ON  ETHACRYNIC ACID/CN
L2             1 SEA ABB=ON  PDTC/CN
L3             0 SEA ABB=ON  2,3-DIMERCAPTO-1-PROPANE SULFONIC ACID/CN
L4             1 SEA ABB=ON  2,3-DIMERCAPTO-1-PROPANESULFONIC ACID/CN
L5             1 SEA ABB=ON  DITHIOCARBAMATE/CN
L6             1 SEA ABB=ON  DITHIOTHREITOL/CN
L7             0 SEA ABB=ON  GLUTATHIONE ESTER/CN
L8             1 SEA ABB=ON  BUTHIONINE SULFOXIMINE/CN
L9             1 SEA ABB=ON  METHIONINE SULFOXIMINE/CN
L10            0 SEA ABB=ON  N-ACETYL CYSTEINE/CN
L11            1 SEA ABB=ON  N-ACETYLCYSTEINE/CN
L12            1 SEA ABB=ON  CYSTEAMINE/CN
L13            2 SEA ABB=ON  LIPOIC ACID/CN
L14            1 SEA ABB=ON  THIOCTIC ACID/CN
L15            0 SEA ABB=ON  2-MERCAPTO-1-PROPANESULFONIC ACID/CN
L16            3 SEA ABB=ON  DMSA/CN
L17            1 SEA ABB=ON  304-55-2/RN
L18            1 SEA ABB=ON  MESNA/CN
L19            1 SEA ABB=ON  DITHIOTHREITOL/CN
L20            0 SEA ABB=ON  ACIVACIN/CN
L21            1 SEA ABB=ON  ACIVICIN/CN

     FILE 'HCAPLUS' ENTERED AT 17:04:07 ON 17 SEP 2005
L22            1 SEA ABB=ON  ACIVACIN

     FILE 'REGISTRY' ENTERED AT 17:07:30 ON 17 SEP 2005
L23            1 SEA ABB=ON  ACIVICIN/CN
L24           17 SEA ABB=ON  L1 OR L2 OR L4 OR L5 OR L6 OR L8 OR L9 OR L11 OR
                 L12 OR L13 OR L14 OR L16 OR L17 OR L18 OR L19 OR L21 OR L23

     FILE 'HCAPLUS' ENTERED AT 17:08:34 ON 17 SEP 2005
L25        23859 SEA ABB=ON  L24
L26       146867 SEA ABB=ON  L25 OR (?ETHACRYNIC? OR (2,3-DIMERCAPTO-1-PROPANESU
                 LFONIC? OR 2-MERCAPTO-1-PROPANESULFONIC)(W)?ACID? OR ?DITHIOCAR
                 BAMATE? OR ?DITHIOTHREITOL? OR ?GLUTATHIONE? OR (?BUTHIONINE?
                 OR ?METHIONINE?)(W)?SULFOXIMINE? OR N-?ACETYLCYSTEINE? OR NAC
                 OR ?CYSTEAMINE?)
L27       149253 SEA ABB=ON  L26 OR (?LIPOIC? OR ?THIOCTIC? OR 2-MERCAPTO-1-PROP
                 ANESULFONIC?)(W)?ACID? OR DMSA OR MESNA OR ?REDUC?(W)?CYSTEINE?
                  OR ?ACIVACIN? OR ?ACIVICIN?
L28         7586 SEA ABB=ON  L27 AND ?REDOX?
L29         1110 SEA ABB=ON  L28 AND (?CANCER? OR ?CARCIN? OR ?NEOPLAS? OR
                 ?TUMOR? OR ?TUMOUR?)
L30          199 SEA ABB=ON  L29 AND ?PROLIFERAT?
L31           48 SEA ABB=ON  L30 AND ?THIOL?
L32            0 SEA ABB=ON  L30 AND NON?(W)?VIRAL?
L33           57 SEA ABB=ON  L30 AND (?VIRUS? OR ?VIRAL?)
L34           54 SEA ABB=ON  L30 AND (PRD<19990216 OR PD<19990216)
L35           85 SEA ABB=ON  L31 OR L34
L36           54 SEA ABB=ON  L35 AND (PRD<19990216 OR PD<19990216)

     FILE 'MEDLINE, CANCERLIT, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 17:24:57
     ON 17 SEP 2005
L37          103 SEA ABB=ON  L35
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L38          67 DUP REMOV L37 (36 DUPLICATES REMOVED)

     FILE 'USPATFULL' ENTERED AT 17:27:05 ON 17 SEP 2005
L39         808 SEA ABB=ON  L35 AND (PRD<19990216 OR PD<19990216)
L40         316 SEA ABB=ON  L39 AND ?THIOL?
L41         140 SEA ABB=ON  L40 AND ?CHEMOTHERAPEUTIC?(W)?AGENT?
L42           8 SEA ABB=ON  L41 AND NON?(W)?VIRAL?
              SAV L42 SPI435L42/A

     FILE 'HCAPLUS' ENTERED AT 17:29:19 ON 17 SEP 2005
              SAV L36 SPI435L36/A

     FILE 'MEDLINE, CANCERLIT, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 17:29:39
     ON 17 SEP 2005
              SAV L38 SPI435L38/A

     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   16 SEP 2005  HIGHEST RN 863378-74-9
     DICTIONARY FILE UPDATES:  16 SEP 2005  HIGHEST RN 863378-74-9

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     ************************************************************
     *                                                          *
     * The CA roles and document type information have been removed from *
     * the IDE default display format and the ED field has been added,   *
     * effective March 20, 2005.  A new display format, IDERL, is now    *
     * available and contains the CA role and document type information. *
     *                                                          *
     ************************************************************

     Structure search iteration limits have been increased.  See HELP SLIMITS
     for details.

     Experimental and calculated property data are now available. For more
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     to the file summary sheet on the web at:
     http://www.cas.org/ONLINE/DBSS/registryss.html

     FILE HCAPLUS

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strictly prohibited.

FILE COVERS 1907 - 17 Sep 2005 VOL 143 ISS 13
FILE LAST UPDATED: 16 Sep 2005 (20050916/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MEDLINE
FILE LAST UPDATED: 16 SEP 2005 (20050916/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CANCERLIT
FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 15 Sep 2005 (20050915/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE JAPIO
FILE LAST UPDATED: 5 SEP 2005 <20050905/UP>
FILE COVERS APR 1973 TO APRIL 28, 2005

<<< GRAPHIC IMAGES AVAILABLE >>>

FILE JICST-EPLUS
FILE COVERS 1985 TO 13 SEP 2005 (20050913/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 15 Sep 2005 (20050915/PD)
FILE LAST UPDATED: 15 Sep 2005 (20050915/ED)
HIGHEST GRANTED PATENT NUMBER: US6944881
HIGHEST APPLICATION PUBLICATION NUMBER: US2005204445
CA INDEXING IS CURRENT THROUGH 15 Sep 2005 (20050915/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 15 Sep 2005 (20050915/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
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>>> /PK, etc. <<<

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>>> the earliest to the latest publication. <<<

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substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 14 September 2005 (20050914/ED)

FILE RELOADED: 19 October 2003.